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THE EFFECT OF LIGATION ON INFECTION OF THE PATENT DUCTUS ARTERIOSUS*

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Six years ago Gross (Gross and Hubbard, 1939), of Boston, Mass., performed the first successful ligation of a persistently patent ductus arteriosus, and sixteen months later the first ligation of a case complicated by subacute bacterial infection was performed in this country with a successful result (Bourne, Keele, and Tubbs, 1941).

In this communication 9 infected cases treated by ligation are reported, 6 of these patients being well to-day and apparently cured. As so little has been published on this subject in the English literature, the essential anatomy and physiology of the ductus arteriosus and the pathological effects of its persistence, with particular reference to the complication of subacute bacterial infection, are described first.

ANATOMY AND PHYSIOLOGY OF THE DUCTUS ARTERIOSUS

The ductus arteriosus which connects the pulmonary artery at its point of bifurcation to the aorta just distal to the origin of the left subclavian artery is stated to be derived from the sixth left aortic arch. Its function during fœtal life is to convey the major part of the output of the right ventricle directly into the descending aorta, thus by-passing the pulmonary circulation; the blood-flow is therefore from the pulmonary artery to the aorta. In the full-term fœtus the ductus is 1·5 cm. long and appears to be the direct continuation of the pulmonary artery; its diameter (0·75 cm.) approximates to that of the descending aorta (*Fig.* 1). It runs almost parallel to the aorta before opening into it at a very acute angle and is relatively much longer and placed more obliquely to the aorta than the same vessel found in subjects in whom patency has persisted into post-natal life.

The normal time and mechanism of closure of the ductus have been discussed at length from time to time. From autopsy examination of infants, anatomical obliteration of the lumen was found to occur in most subjects within three months, but many authors believed it became impermeable as soon as pulmonary respiration

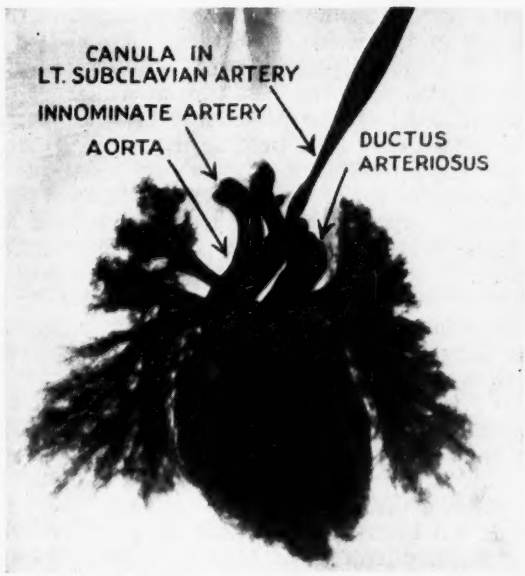

FIG. 1.—Radiograph showing the calibre, length, and position of the ductus arteriosus at birth. Preparation obtained by filling the heart and large vessels of a full-term stillborn fœtus with iodide solution through the left subclavian artery. The aorta has been ligated just distal to the entrance of the ductus.

was established. In 1939 Barclay, Barcroft, and their co-workers, using sheep fœtuses, obtained X-ray cinematographic films of the region of the heart and great vessels after injection of radio-opaque substance into the external jugular vein and produced beautiful graphic demonstration of the functional closure of the ductus shortly after delivery—within five minutes in one experiment. More recently, Kennedy and Clark (1941) have shown from their observations on guinea-pig embryos that this is due to contraction of the muscular wall, the ductus being very rich in

* The basis of this communication was delivered as a Hunterian Lecture at the Royal College of Surgeons on April 28, 1943.

smooth muscle compared with the elastic tissue structure of the neighbouring vessels. Subsequent anatomical obliteration is essentially the result of sub-endothelial cicatrization and is frequently complete at the end of a month.

THE EFFECTS OF PATENCY PERSISTING IN POST-NATAL LIFE

In the normal individual, as soon as pulmonary respiration is established, the pressure in the aorta is raised considerably above that in the pulmonary artery, so that, if the ductus remains patent, blood will flow in a rapid stream from the aorta into the pulmonary artery and, as this involves a shunt of arterial blood into a venous stream, there will be no cyanosis. But Maude Abbott (1936) pointed out that cyanosis may appear under conditions causing sufficient rise of pulmonary pressure to produce a temporary reversal of flow, e.g., prolonged crying, violent physical exertion, or in terminal heart failure; and, further, that if the ductus is acting as a compensatory mechanism to one or more other congenital cardiac abnormalities, cyanosis will be present under *resting* conditions.

Where ductal patency is the only abnormality (and this alone is the condition in which we are concerned here), the pulmonary artery becomes dilated and may later become the site of atherosclerosis as a result of the pressure being raised above that of the normal individual, and the right ventricle hypertrophies in response to the increased work of pumping blood against this raised pressure. The left ventricle also hypertrophies as its output has to be increased to compensate for diversion of part of the stream into the pulmonary circulation. Even so, the peripheral circulation may be so diminished as to result in retarded development and nutrition. According to Eppinger and Burwell (1940), from 45 per cent to 75 per cent of the blood put out by the left ventricle passes through the ductus into the pulmonary artery.

It has been suggested that the blood-volume is increased analogous to that which Holman (1937) has shown to occur with arteriovenous aneurysms of the systemic circulation. If this were true, one would expect a greater degree of hypertrophy and dilatation of the heart than is usually seen. One would also expect an immediate slowing of pulse-rate on ligation and a post-operative diuresis with hæmoconcentration. In the 9 cases to be described, slowing of the pulse-rate at the time of ligation has been exceptional, and no post-operative diuresis has been observed. (In an uninfected case, not included in this series, operated on because of early heart failure, immediate slowing of the pulse-rate and post-operative diuresis did occur, but the increased blood-volume may well be explained on the grounds of heart failure *per se*.)

As referred to previously, the persistently patent ductus differs from that found at birth, being relatively shorter (usually less than 1·5 cm.), of variable diameter (average 1 cm.), but generally wider at its aortic and pulmonary attachments than in the middle, and opening into the *under* surface of the aortic arch. It may have no length at all, rather like a gastro-enterostomy stoma—the so-called 'window type'. Although usually outside the pericardial reflection, in 2 of the 9 cases to be described the medial and anterior surfaces were covered by serous pericardium.

The frequency of complicating subacute bacterial infection is unknown; 29 per cent of the 73 cases over the age of 2 described by Maude Abbott (1936) were infected, but such autopsy statistics give an exaggerated idea of its frequency. It is almost unknown before the age of 6 and uncommon before puberty, the maximum incidence lying between 16 and 25 (Hubbard, Emerson, and Green, 1939). The vegetations occur primarily in the pulmonary end of the ductus, subsequently spreading into the pulmonary artery: sometimes they are found at a very early stage on the anterior wall of the pulmonary artery, a region which is probably under constant strain from the impact of the blood flowing through the ductus. Later, the vegetations may extend back to the pulmonary valve and also involve the aortic end of the ductus or affect other valves. As the vegetations occur primarily in the pulmonary end of the ductus, it is a natural sequence that embolic phenomena in the lungs should precede those in the systemic circulation. The inflammatory process is not confined to the intima of the affected region, but may extend right through the wall into the perivascular tissue and, as a result, the ductus itself may become the site of aneurysmal dilatation (Schlaepfer, 1926). Consequently, surgical isolation of the infected ductus from the surrounding tissues must be expected to be more difficult and hazardous than in the uninfected case.

In the past the prognosis after the supervention of infection has been fatal with exceedingly few exceptions, the duration of life after the onset of infection varying from one month to two years. There are only 2 cases on record (Chester, 1937; Touroff and Tuckman, 1942) in which recovery has taken place without operation, and infection recurred in 1 of these twelve years later.

DETAILS OF 9 INFECTED CASES TREATED BY LIGATION, WITH DESCRIPTION OF SURGICAL TECHNIQUE EMPLOYED

In October, 1939, a man of 23 was admitted to St. Bartholomew's Hospital with a patent ductus complicated by subacute bacterial endarteritis. Dr. Keele, the physician in charge, asked me to consider ligating the ductus with the idea that it might be possible to close the vessel at its aortic end and again at the pulmonary end and that this might exclude the vegetations from contact with the circulating blood. He also suggested that it might be possible to divide the

ductus between the ligatures and remove the vegetations. Strieder (Grabiel, Strieder, and Boyer, 1938) attempted such an operation in March, 1937, on a similar patient and with the same idea, but he found the ductus so adherent that he was unable to pass a ligature behind it. He tried to obliterate the lumen with a series of plicating sutures, but was not completely successful in accomplishing this. This patient died on the fourth day after operation from acute dilatation of the stomach, and at autopsy vegetations were found to extend back to within 1 cm. of the pulmonary valve; on this account Strieder and his co-workers concluded that the operation had no chance of being successful in this case. Incidentally the ductus turned out to be of the 'window type', which, from the technical viewpoint, was exceedingly bad luck. Later Gross (1939) demonstrated the feasibility of the operation *in the absence of infection* by his report of 4 consecutive successful results.

On these facts and theories we had to decide whether operation was justified in the presence of infection. In view of the almost hopeless prognosis, and after explaining the experimental nature of the operation to the relatives, we decided to attempt ligation and this patient has turned out to be the first successful case yet reported.

As certain points referable to surgical technique arise in the case reports, the steps of the operation need description first.

SURGICAL TECHNIQUE OF LIGATION

The technique employed has been very similar to that originated and described in detail by Gross (1939, 1940) for uninfected cases.

All the patients received intravenous glucose-saline and sometimes blood during the operation. If the suggestion (previously mentioned) that these patients have an increased blood-volume were true, intravenous fluid would be contra-indicated, although it might be wise to give it at a rate just sufficient to prevent thrombosis so that blood-loss could be immediately replaced in case of severe accidental hæmorrhage. But I am not convinced that the blood-volume is increased. One patient, who appeared clinically in need of transfusion at the end of the operation, but in whom blood-loss had not been severe, improved rapidly as soon as blood was given.

With the exception of *Case* 1, all the patients have been anæsthetized with a mixture of cyclopropane and oxygen given through an ordinary face-piece by Mr. Rait Smith, for whose help I am extremely grateful. Such anæsthesia produces very quiet shallow respiration and therefore minimal movement of the operative field and yet obviates even the slightest degree of anoxæmia.

With the patient lying on his back with the left arm held in abduction, the skin incision is made over the second left intercostal space and extends from the midline in front to the anterior axillary line (*Fig.* 2). A short vertical limb placed centrally over the sternum facilitates retraction later. Pectoralis major is split in the line of its fibres and that part exposed separated from its sternocostal origin. Pectoralis minor is

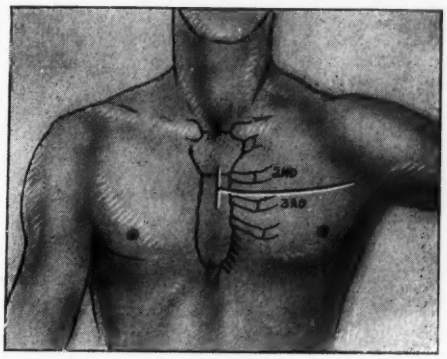

FIG. 2.—The skin incision.

divided obliquely across its fibres. The medial ¾ in. of the second and third costal cartilages are excised together with their perichondrium (*Fig.* 3). The pleural cavity is then opened through the second intercostal space, the incision stopping short of the internal mammary vessels. By raising the medial ends of the divided ribs, exposure for double ligation of these vessels is obtained, the ligatures serving to control hæmorrhage from small branches: division of the main vessels between the ligatures does not increase the exposure and has therefore been abandoned. After protection of the wound edges with moist gauze pads, the space is opened up with a single rib-spreader (*Fig.* 4).

This gives full exposure of the region below the aortic arch and the enlarged over-expansile pulmonary artery with a very marked thrill is readily recognized. The mediastinal pleura immediately behind the phrenic nerve and below the aortic arch is picked up with a long clamp and incised vertically. With the exception of one case in which the ductus was almost entirely within the pericardial sac, no difficulty has been experienced in identifying the ductus.

The cellular tissue under the arch of the aorta is gently swept from the anterior surface of the ductus with a pledget of gauze held in a long hæmostatic clamp; this separation is continued by blunt dissection until only the posteromedial surface remains to be freed. The fibro-fatty material surrounding the ductus contains numerous small blood-vessels and one or more hyperæmic lymphatic glands, but a plane of cleavage has usually been found without great difficulty or troublesome bleeding (*Fig.* 5). The next step—that of freeing the posteromedial surface of the ductus—is the most difficult and worrying part of the operation, for it cannot be done under direct vision. The left index finger is inserted into the cleft between the aortic arch and the

bifurcation of the pulmonary artery and in front of the ductus, and a malleable blunt-ended aneurysm needle is passed through the tissues behind the ductus so as to impinge on the left index finger, finally bringing the eye of the needle into view to receive the ligature material. Because of the frequent extension of inflammatory changes through all the coats of the ductus and of the possibility of actual aneurysmal dilatation, it must be obvious that this manœuvre is more likely to cause accidental hæmorrhage than any other during the operation and must therefore be carried out with the greatest care and gentleness. The left recurrent laryngeal nerve, which is readily seen, undoubtedly receives some pressure and possibly stretching; as a result, 2 of this series of 9 cases suffered from temporary post-operative hoarseness. As the infection involves predominantly the pulmonary end of the ductus, it is wise to isolate the aortic end first. In no case has the ductus been more than 1·5 cm. long, the average being about 1 cm. Estimation of the diameter is difficult, but this also has appeared to average 1 cm. It is therefore a short wide channel. No. 5 tubular silk has been used as ligature material, two strands being passed through the eye of the aneurysm needle and each brought through double. The ductus is ligated as near to its pulmonary end and aortic end as possible, each ligature being formed of two strands of silk. In some cases the first ligature has greatly reduced but not abolished the thrill in the pulmonary artery, but the second has always completed its destruction. The ligatures have never been placed more than 0·75 cm. apart and often less than this, so that division of the vessel between them would almost certainly have precipitated fatal hæmorrhage. The mediastinal pleura is left unsutured as it is considered preferable for any exudate to escape into the pleural cavity. The chest is finally closed in layers. If the patient is in good condition the lung is

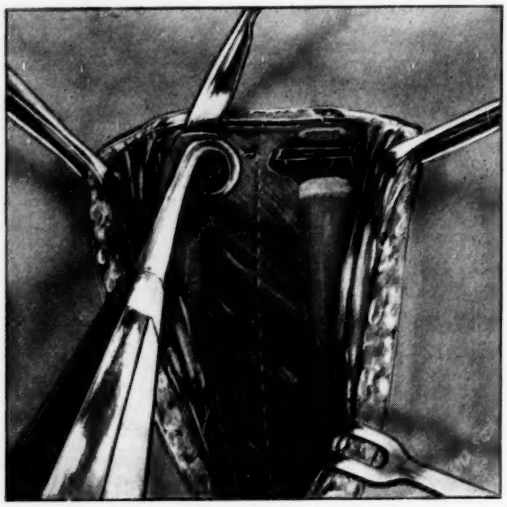

FIG. 3.—The second intercostal space exposed (viewed from the left side of the patient as by the surgeon).

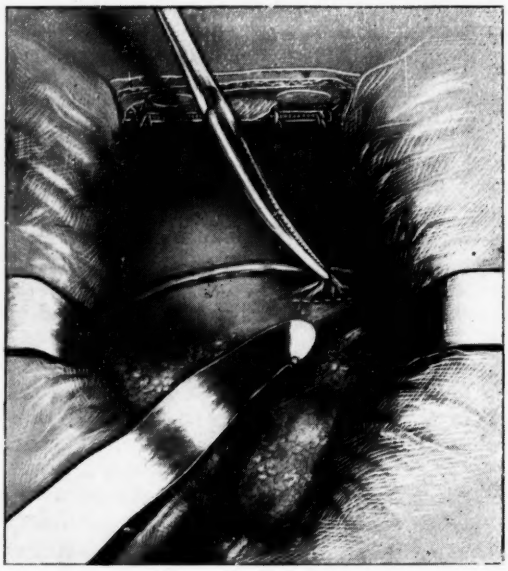

FIG. 4.—Pleural cavity opened and lung depressed under a lighted retractor. The mediastinal pleura has been picked up below the aortic arch and behind the phrenic nerve.

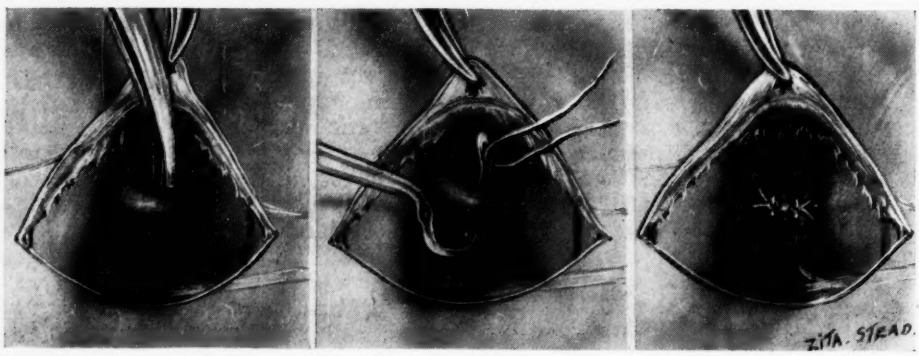

FIG. 5.—Stages in isolation and ligation of the ductus. The proximity of the recurrent laryngeal nerve after leaving the vagus is shown.

inflated by the anæsthetist using gentle positive pressure before the wound is rendered air-tight, but aspiration with a pneumothorax apparatus after the operation has been completed is likely to put less strain on the circulation.

CASE REPORTS

(The first 2 cases have been previously reported —Bourne, Keele, and Tubbs, 1941.)

Case 1.—A man of 23—the case already referred to—was admitted to hospital in October, 1939, complaining of fever, weakness, and loss of weight. He knew that he had an abnormality of the heart dating from birth, but he had been perfectly well and capable of all activities until five months previously when he had so-called "flu". He had run an intermittent fever ever since and lost 2 st. in weight.

ON EXAMINATION.—He appeared thin and very pale, but without cyanosis. Numerous petechiæ were present on the neck, shoulders, and legs. There was slight cardiac enlargement and he had the classic signs of a patent ductus, a thrill extending through systole into diastole being palpable at the pulmonary base and a loud 'machinery' murmur occupying the whole of systole and a large part of diastole, being audible all over the precordium but with its maximum intensity at the pulmonary base. The blood-pressure varied between 110/60 and 150/80, the diastolic pressure being higher than that characteristically found with a patent ductus. The spleen was palpable. Renal embolism was evident by the discovery of much albumin, red cells, leucocytes, and casts in the urine, and renal insufficiency indicated by a blood-urea of 71 mg. per cent. Blood-culture revealed an atypical *Hæmophilus influenzæ*. A teleradiogram showed slight enlargement of the heart and prominence in the region of the pulmonary artery.

For two weeks following admission he ran a high intermittent fever uninfluenced by general medical treatment or blood transfusion. Sulphapyridine was then given, starting with 3 g. daily for three days and continued until the time of operation eighteen days later with 1·5 g. daily: this produced dramatic subsidence in fever and improvement in the general condition, but blood-culture remained positive for the same hæmophilus.

On Dec. 5 the ductus was ligated, the blood-pressure rising from 108/60 to 120/80 at the moment of ligation. The thrill was abolished by the operation and the added sounds changed to a short rough systolic murmur at the pulmonary base.

The post-operative course was seriously complicated by a severe degree of renal failure, but he survived this and remained afebrile with a sterile blood-culture for three and a half months without any sulphonamide therapy. At the end of this period, blood-culture again became positive and more sulphapyridine was given. Six months after operation, he was up and about, and stated that he had never felt better in his life, but the same organism was again found in his blood. Two months later, however, his blood was sterile and has remained so ever since. After nine months in hospital he was discharged and returned to work. At the present time he remains well, except for occasional headaches which he ascribes to migraine.

This case was a great encouragement, but his recovery was not proven to be the result of ligature of the ductus, particularly in view of bacteria being found in the blood so long afterwards.

Case 2.—A girl of 19 was admitted to hospital on Oct. 2, 1940. She had always known that there was something "wrong with her heart", but had been in good health until four months before admission, when she started to complain of headache, lassitude, sweating at night and fever. Ten days before coming into hospital she had left-sided pleuritic pain.

ON EXAMINATION.—She did not look ill, but the temperature rose to 100–101° F. each evening. The apex beat was 1 in. outside the mid-clavicular line: the typical systolic murmur and thrill of a patent ductus were present, both persisting well into diastole and most marked in the second left interspace near the sternum. The blood-pressure was 132/40. The spleen was not palpable. The urine was normal. Blood-culture yielded a growth of *Str. viridans* in all tubes on three separate occasions, colony-count in shake culture numbering at first about 300 per c.c. A teleradiogram showed slight enlargement of the heart and prominence of the pulmonary artery: ill-defined shadows in both lung fields, but particularly the right, were also seen, and the possibility of tuberculous infection mooted, but it was thought that they more probably represented areas of infarction, a fact which was confirmed at operation.

After one week in hospital, sulphapyridine was started and resulted directly in disappearance of fever and later in sterility of the blood. After twelve days without fever the ductus was ligated. This caused an immediate rise of blood-pressure from 132/40 to 154/122, but this later settled to 134/74: however, the murmur, including that part extending into diastole, persisted, although less loud than before operation. Gross (1940) has observed this occasionally in his uninfected cases and supposes that it indicates incomplete obliteration of the channel, but Touroff (1940) reported it in one of his infected cases in which accidental hæmorrhage at the time of operation necessitated *division* of the vessel between ligatures.

A persistent diastolic murmur is difficult to explain if the lumen of the ductus has been completely obliterated, and yet the maintained rise of diastolic pressure and the decrease in the size of the heart and in the prominence of the pulmonary artery seen in radiographs taken later of this patient certainly suggest that obliteration was obtained. However, the convalescence was smooth and the patient put on 1 st. in weight during the first post-operative month. Sulphapyridine therapy was continued for six weeks and the blood kept sterile. When seen recently she was in excellent health and the diastolic fraction of the murmur was only just audible.

Case 3.—A girl of 17 was transferred for operation on Oct. 22, 1941. She was known from childhood to have a so-called "weak heart", but she had been perfectly well until ten weeks before admission, when she had some teeth extracted and subsequently felt "run down" and feverish; later she developed left-sided pleuritic pain.

ON EXAMINATION.—She looked pale and ill: the temperature rose to 101° F. each evening and the pulse-rate was consistently in the region of 120. The classic signs of a patent ductus were found and the blood-pressure measured 116/58. There was no objective evidence of embolism, but shake cultures of the blood grew 143 colonies of a *Str. viridans* per c.c. Sulphapyridine administration caused temporary subsidence of fever and sterility of the blood, but after a week fever and bacteriæmia returned and persisted in spite of various sulphonamides.

On Dec. 4, 1941, the ductus was ligated in spite of the patient being very ill at this time. At operation

infarcts could be seen in the left lung. The ductus was difficult to isolate owing to adhesions and was torn on its anterior wall while clearing the posterior surface,

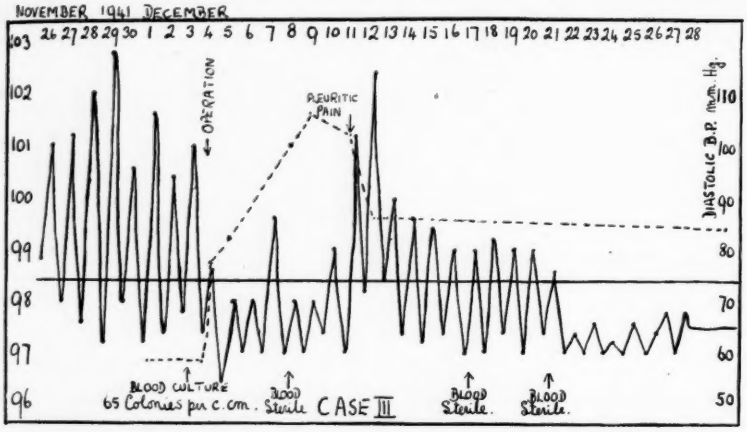

FIG. 6.—*Case* 3. Temperature chart showing the effect of operation. The results of blood-culture are shown below and the dotted line represents the diastolic blood-pressure.

but the bleeding was easily controlled with a clamp. A dark discoloration and induration of the wall of the left branch of the pulmonary artery were accepted as evidence of vegetations in this position. Seven hours after operation the blood-pressure was 100/76, but later became stabilized at 110/84. As in all the later successful cases the thrill and 'machinery' murmur were abolished, a faint systolic murmur remaining at the pulmonary base. The patient immediately became afebrile and blood taken on the second post-operative day and subsequently was sterile. Apart from sudden pleuritic pain on the left side on the seventh day with rise of temperature to 102° F., presumably due to a pulmonary embolus, the patient had a smooth convalescence (*Fig.* 6).

This girl reports that she remains perfectly well (May, 1944). This case is a good example of the success of ligation after failure of the sulphonamides even to control the fever.

Case 4.—A girl of 10 was received for operation on Dec. 12, 1941. The presence of a patent ductus had been diagnosed at the age of 4, but she had been perfectly well until the present illness started four and a half months previously with vomiting and fever rising to 103°–104° F. each day. She had been treated with intravenous heparin together with sulphapyridine, and, later, by combined venesection and transfusion. The sulphonamide treatment caused the fever to subside for a few days, but the blood did not become sterile and the pyrexia was subsequently uninfluenced by sulphapyridine. When transferred for operation, she looked exceedingly ill, pale, and emaciated. The temperature swung daily between 98° and 104° F. and the pulse varied from 100 to 150. There was extreme arterial pulsation in the neck and a systolic thrill could be felt in the suprasternal notch. The classic signs of a patent ductus were present and the blood-pressure measured 106/56. The spleen was considerably enlarged and the urine contained red cells, white cells, and casts. Blood-culture yielded 130 colonies of a *Str. viridans* per c.c. A radiograph suggested cardiac enlargement, and 'fluffy' shadows could be seen scattered throughout both lung fields, but the child was too ill to sit up for a satisfactory picture.

Six days after admission the ductus was ligated. Great difficulty was experienced in finding a plane of cleavage behind the vessel and an aneurysm needle finally had to be forced through the tissues to get the ligatures round. The operation caused little disturbance and the fever immediately subsided, but blood taken four days after operation yielded 7 colonies of a *Str. viridans* per c.c. For four weeks the temperature remained normal except for two short bouts of pyrexia associated with pain in the chest, presumably caused by pulmonary embolism. But then the diastolic fraction of the murmur, which had disappeared following ligation, reappeared with increasing intensity, although it never became as loud as before. At the same time the temperature returned to its previous high levels and the child died eight weeks after operation.

At autopsy multiple infarcts were found in the lungs. The aortic opening of the ductus was widely patent and led into an aneurysm of this vessel about the size of a golf-ball: the ligatures, still tied, were found in the anterior wall of this aneurysm (*Fig.* 7). The pulmonary opening of the ductus was blocked by a huge sausage-shaped

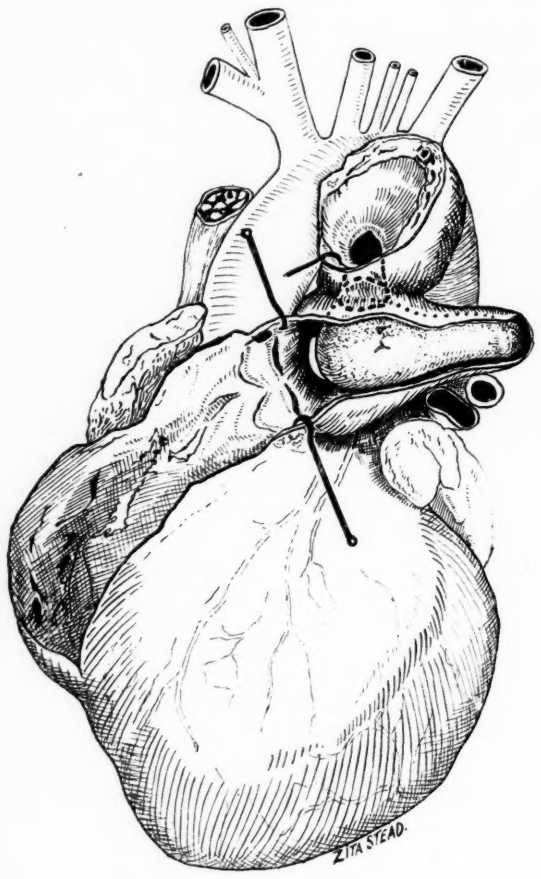

FIG. 7.—*Case* 4. Drawing of heart and main vessels as seen at autopsy (*see* text).

thrombus which lay horizontally in the two branches of the pulmonary artery almost occluding them and containing innumerable Gram-positive cocci. The kidneys showed embolic nephritis and the spleen was enlarged.

I believe the most likely explanation of the clinical and pathological findings is that the posterior wall of the ductus was damaged at operation by the passage of the ligatures, which subsequently cut through, thereby re-establishing the lumen of the ductus. The ligatures were thus left encircling the anterior wall only and this became progressively aneurysmal.

Case 5.—A woman of 29 was admitted on Jan. 12, 1942, complaining of recurrent fever, shortness of breath, and pain in the right shoulder. Congenital heart disease had been discovered at the age of 3, but she had been symptomless until eighteen months previously when she had unexplained fever lasting a month. At this time clinical and radiological signs of a right basal pleurisy were found, but two blood-cultures were sterile. She remained well for nearly a year after this, but then had another febrile attack and remained in bed at home for four weeks. Two months later the fever and right-sided pleurisy recurred and she became short of breath.

ON EXAMINATION.—She did not look seriously ill, but the temperature rose to 100° or 101°F. each evening, and the pulse-rate averaged 110. The classic signs of a patent ductus were present and the blood-pressure measured 102/58. The signs of either a high right diaphragm or basal pleural effusion were found and the tip of the spleen was palpable. The urine was normal. Blood-culture yielded 86 colonies of a *Str. viridans* per c.c. X-ray films of the chest showed a high right diaphragm, no cardiac enlargement, and little, if any, enlargement of the pulmonary artery.

The ductus was ligated on Feb. 2, which caused the diastolic blood-pressure to rise from 58 to 88. An enlarged gland adjacent to the ductus was excised

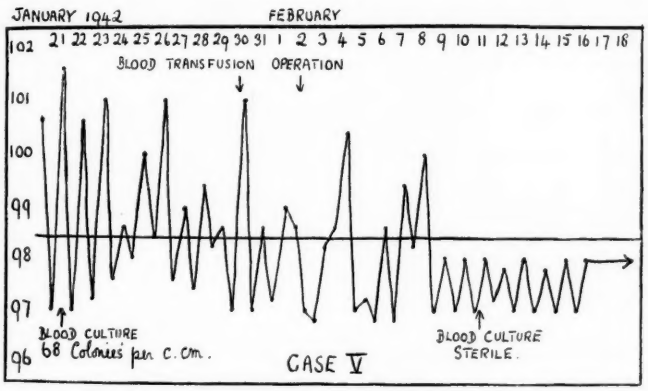

FIG. 8.—*Case* 5. Temperature chart showing the effect of operation. No sulphonamide was given.

and a bacteriological culture made from it, but this was sterile. The operation abolished the diastolic fraction of the murmur, but a systolic murmur remained. The immediate post-operative period was marred by collapse of the left lower lobe, but this cleared up rapidly. Nine days after operation the blood was sterile. She has remained in good health ever since and, when seen in April, 1943, volunteered that she could exert herself with less breathlessness than ever before.

This case was treated surgically without any pre- or post-operative sulphonamide therapy, so that the effect of the operation alone might be more accurately assessed (*Fig.* 8).

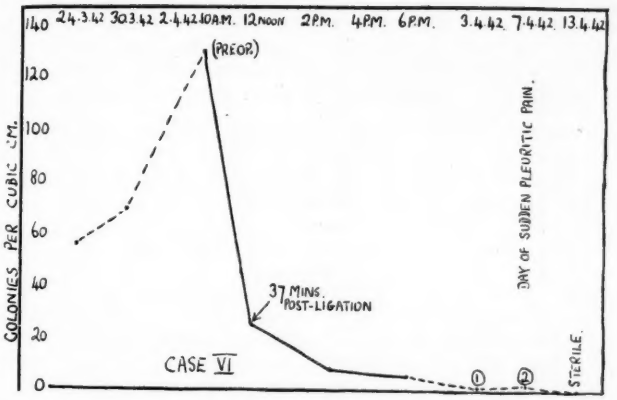

FIG. 9.—*Case* 6. Graph showing the *immediate* effect of ligation on colony counts obtained from blood-cultures.

Case 6.—A woman of 22 came into hospital on March 23, 1942, complaining of left-sided pleuritic pain. She had no previous knowledge of heart disease and had always been capable of normal activities. Five months before admission she had some teeth extracted and felt weak for several days afterwards, but returned to work. A month later she again felt weak and attended her doctor, who told her she had valvular disease of the heart and anæmia. After another month she developed right-sided pleurisy and became short of breath. The pleuritic pain recurred four weeks and again six weeks later: on the second occasion (two weeks before admission) she had fever up to 103° F., felt tired, and suffered from palpitations. There had been amenorrhœa for four months.

ON EXAMINATION.—She looked sallow and the temperature rose to 102° or 103° F. each evening. The classic signs of a patent ductus were present and the blood-pressure measured 125/50. The percussion note was impaired and the air entry diminished at the right base. The spleen was not palpable. The urine contained blood, but there was no other evidence of systemic embolism. Blood-culture yielded 56 colonies of a *Str. viridans* per c.c. A teleradiogram showed fullness of the upper part of the left border of the heart and an ill-defined loss of translucency in the right lower lung field. Sulphanilamide lowered the fever for four days, but subsequently had no effect and was therefore omitted.

The ductus was ligated on April 2; this caused a rise of diastolic blood-pressure to 80 and did away with the thrill and diastolic murmur. The most interesting observation made from this operation was the amazing rapidity with which the bacteria were removed from the blood-stream as a result of ligation, for blood taken immediately *before* operation grew 130 colonies of a *Str. viridans* per c.c., whereas that taken thirty-seven minutes *after* ligature yielded 26 colonies, that four hours after 8 colonies, that seven hours after 5 colonies, and that taken next morning only 1 colony per c.c. (*Fig.* 9).

The convalescence was uneventful except for a lesion of the upper trunk of the left brachial plexus which dated from the time of operation and took three months to clear up completely; this complication was undoubtedly caused by stretching of the plexus as a result of inadequate support of the abducted arm. The patient also had sudden pleuritic pain on the fifth post-operative day with a rise of temperature to 102° F., and blood taken on this day grew 2 colonies of *Str. viridans* per c.c. The patient became afebrile on the ninth day and blood-culture was sterile on the eleventh day. She has kept in good health ever since.

Case 7.—A man of 26 was transferred for operation on April 13, 1942. He had known for many years that he had a congenital abnormality of the heart, but, apart from osteomyelitis of the jaw five years previously, had been perfectly well until Christmas, 1941, when he had "gastric flu" associated with fever which persisted. At the end of January, 1942, he had sudden severe pain in the left thigh and was admitted to hospital fourteen days later. A diagnosis of subacute bacterial endarteritis superimposed on a patent ductus was made and he was treated by repeated blood transfusion, antitoxin serum, and sulphapyridine, but, in spite of all therapy, continued to run an evening pyrexia between 100° and 104° F. After receiving a blood transfusion of 2½ pints on March 28, 1942, he had severe precordial pain, and the heart, already enlarged, became greatly dilated.

On Examination.—He looked pale and ill: there was no cyanosis, but he was orthopnœic and very short of breath. There was marked pulsation with a systolic thrill at the suprasternal notch, and this thrill could also be felt, although less well, in the second left intercostal space. The apex beat was situated 6 in. from the midline and a rough systolic and diastolic murmur could be heard all over the precordium, with its maximum intensity in the pulmonary area. The blood-pressure was 146/40. Scattered rhonchi and râles were heard over both lungs with large numbers of fine râles at both bases. The liver and spleen were enlarged, but there was no peripheral œdema. The urine contained numerous red cells. Blood-culture yielded 127 colonies of a *Str. viridans* per c.c. It was clear that we were faced with a new problem, for this patient had advanced left-sided heart failure in addition to subacute bacterial endarteritis and the risk of ligation would obviously be greater than in the previous cases. However, it seemed equally clear that he should be given the chance which operation might offer and the ductus was therefore ligated on April 23. It was found in a very medial position, covered by serous pericardium on its anterior and medial surfaces: the pericardium was opened but an aneurysm needle could not be passed round the postero-medial surface of the ductus and the ligature was ultimately passed on a curved round-bodied needle. During all this manipulation the patient's condition remained satisfactory. The systolic blood-pressure rose to 222 during the first thirty minutes of the operation and remained in the region of 200 until the ligature was tied. At this moment the diastolic pressure rose from 60 to 80, but that in systole fell rapidly and the pulse became feeble and irregular.

When the operation had been completed, the patient was pale and cyanosed, and the pulse rapid and feeble. Morphine was injected to control his restlessness and oxygen administered, but the patient died 45 minutes after completing the operation. At autopsy the right ventricle was dilated but did not appear hypertrophied, whereas the left ventricle showed considerable hypertrophy. A pedunculated partially-organized vegetation containing Gram-positive cocci was found on one aortic cusp. Vegetations were also present in the bifurcation and left branch of the pulmonary artery. There was induration at the site of the ductus due to fibroblastic granulation tissue, but no organisms were demonstrated in this material. The ligature, which had closed any visible lumen in the ductus, was found to have been passed through the medial part of the lumen of the vessel, but no blood leak had resulted. There were several old infarcts in the lungs and the kidneys showed embolic nephritis. The liver and spleen were both grossly enlarged and congested, the liver showing typical 'nutmeg' change. If this man had not succumbed to acute heart failure as a result of the ligation, I think it is certain that he would not have recovered from the infection owing to the vegetation on an aortic cusp.

Case 8.—A man of 33 was admitted on March 1, 1943, complaining of weakness, fever, and loss of weight. He had known from the age of 14 that he had a congenital abnormality of the heart and had therefore avoided the more strenuous forms of exercise; however, he had been able to cycle, dig, etc., with only slightly more breathlessness than that experienced by the normal individual. Early in December, 1942, circumcision had been performed and the wound took a month to heal. A month after the operation, he started severe night sweats and became extremely fatigued. After six weeks he was admitted to hospital where he was found to have the classic signs of a patent ductus, high fever, and a palpable spleen. Blood-culture had yielded a growth of a *Str. viridans* and *Staph. aureus*. He developed right-sided pleuritic pain following admission. Sulphathiazole was given and his fever subsided: the drug was continued until the time of transfer for operation, by which time he had lost 3 st. in weight.

On Examination.—He appeared pale and ill; the pulse was of Corrigan type, the blood-pressure measuring 146/54. Blood-culture was sterile. A teleradiogram showed no enlargement of the heart, but prominence of the pulmonary artery. Sulphathiazole was discontinued and for three days the temperature only reached 99·8° F. in the evening. High fever then recurred and blood-culture yielded an unidentifiable Gram-negative bacillus. Sulphathiazole was restarted, but, after causing an initial reduction in fever, failed to have any influence.

The ductus was ligated on March 15. The passage of the ligatures necessitated opening the pericardial sac as the anteromedial wall of the ductus was clothed with the membrane. There was an excess of pericardial fluid, and œdematous adhesions were present in the region of the ductus. The pericardium was left unsutured. An electrocardiogram was taken during the operation and a normal tracing obtained fifteen minutes before and after ligation, but that taken one minute after ligation showed numerous extrasystoles. Blood taken immediately before operation grew 25 colonies of a coagulase-negative *Staph. albus* per c.c., whereas that taken thirty minutes after completion grew 6 colonies of the same organism per c.c., and blood taken three hours and again six hours after was sterile. However, the nature of the infecting organisms found in this case has been so variable that it would seem unwise to stress these findings. The thrill and diastolic murmur were entirely abolished by the operation and the diastolic blood-pressure raised to a minimum of 76. Severe precordial pain and loud pericardial friction occurred the day following

surgery and lasted for forty-eight hours—undoubtedly the result of opening the pericardial sac. During the first two weeks he developed left-sided pleuritic pain with signs of consolidation over the left lower lobe, and abdominal pain with diarrhœa and mucus-containing stools, the more acute phases of these complications being accompanied by fever up to 103° F. It is

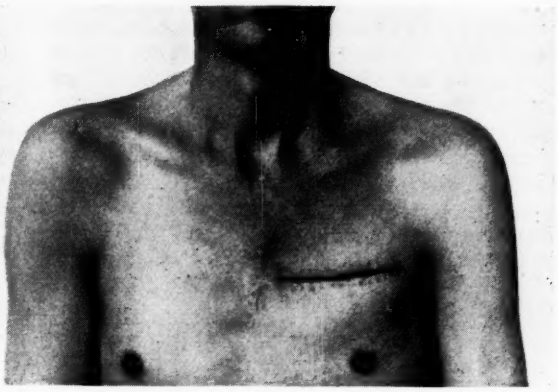

FIG. 10.—*Case* 8. Photograph of wound six weeks after operation.

probable that the pulmonary lesion was the result of embolism, but doubtful if the abdominal symptoms had the same aetiology. Subsequently he became afebrile and has remained perfectly well ever since (*Fig.* 10).

Case 9.—A girl, aged 15, was transferred for operation on April 22, 1943. She was known from early childhood to have a patent ductus and, as a result, had lead an extremely sheltered life. However, she had been in her normal health until a month before transfer, when she developed a cough with yellow, sometimes blood-streaked, sputum and upper left pleuritic pain. She was admitted to hospital on March 30 and was found to be febrile (temperature 103° F.) with a respiratory rate of 35 and to have signs of consolidation in the left upper chest. The white blood-count was 21,400 per c.mm., and a radiograph showed a large opacity in the left upper lobe extending down to the hilum and obscuring the region below the aortic arch. A diagnosis of pneumonia was made and she was treated with sulphamezathine and, later, sulphadiazine without obvious effect on the fever, but the radiological opacity gradually shrank and showed evidence of excavation. On April 14 blood-culture grew a *Str. viridans* and the diagnosis was amended to subacute bacterial infection complicating a patent ductus, but it was not clear whether this was secondary to the pulmonary infection or the pulmonary consolidation secondary to a large embolus.

ON EXAMINATION.—She looked pale, sallow, and thin, but no petechiæ could be found. The temperature rose each evening to between 100° F. and 103° F. The classic signs of a patent ductus were present, but no abnormal signs were found at this time in the lungs. The blood-pressure measured 120/55. The spleen was not palpable and the urine was normal. Shake cultures of the blood yielded 54 colonies of a *Str. viridans* per c.c. and examination of the sputum showed the same organism predominating. A teleradiogram showed an elongated opacity underlying the second rib in front and extending from the left hilum to the chest wall: this still obscured the upper part of the left border of the heart and showed cavitation peripherally: a clearly-defined oval opacity at the right hilum was interpreted as an enlarged gland.

The ductus was ligated on May 3. Technically this was by far the most difficult yet tackled as the upper lobe was densely adherent to the chest wall along the second rib, and these adhesions continued on to the mediastinum below the aortic arch, obscuring the anatomy so much that identification of the ductus almost entirely depended on palpation: dissection was also made difficult by œdema, induration, and increased vascularity of the tissues. Nevertheless, the operation was completed without accident and the diastolic bruit entirely disappeared. Initially both systolic and diastolic pressures were low as a result of shock, but a week after operation the diastolic pressure measured 78 (pre-operative, 55). Blood-culture taken immediately before operation grew 97 colonies of *Str. viridans* per c.c., whereas that taken immediately after grew 5 colonies and that taken ten hours after 6 colonies per c.c. Repeated pulmonary embolism with rigors occurred during the two weeks following operation, but the temperature then settled to below 99° F. and blood-culture on the sixteenth post-operative day was sterile. Alas! this encouragement was short-lived, for at the end of a month the temperature returned to its previous remittent, or intermittent character, blood-culture grew large numbers of *Str. viridans*, repeated *peripheral* embolism occurred (no further pulmonary embolism was detected), and a soft diastolic murmur of aortic type developed. The girl finally died nearly four months after operation.

At autopsy, the heart showed slight enlargement affecting the two sides equally. The valves of the right side appeared normal, but both the mitral and aortic cusps were thickly covered with large friable vegetations containing innumerable streptococci; the valves did not show any evidence of congenital malformation or *chronic* inflammatory change. The aortic and pulmonary ends of the ligated ductus, the lumen of which was completely obliterated, were represented by shallow depressions with a smooth floor and devoid of thrombus. In the left pulmonary artery immediately lateral to the pulmonary attachment of the ductus there was a considerable amount of firm thrombus which covered over the opening of a saccular aneurysm 1·5 cm. in diameter and lying between the distal part of the aortic arch and the left pulmonary artery: this aneurysm was filled with very firm laminated clot. At the site of bifurcation of the right pulmonary artery there was another larger saccular aneurysm which was also filled with laminated clot. Microscopical examination of the thrombi in the two aneurysms and in the left branch of the pulmonary artery showed that they were of similar laminated structure and free from bacteria. There were numerous old infarcts in the lungs and cavitation with surrounding consolidation in the left upper lobe; this cavitation probably resulted from liquefaction of a large infarct as there was much blood-pigment in the surrounding tissue. The spleen, which was enlarged, and both kidneys showed infarction, undoubtedly secondary to the left-sided valvular vegetations.

Co-ordination of the clinical and pathological findings in this case is much complicated by the discovery of the aneurysms of each branch of the pulmonary artery. The aneurysm of the right branch was certainly present before operation as it showed as an oval opacity at the right hilum in a pre-operative X-ray picture (although, at the time, this shadow was falsely interpreted as an enlarged gland). It is probable that the small aneurysm of the left branch also pre-existed operation as retrospective examination of the same X-ray film reveals a shadow compatible with its presence although much obscured

by the opacity extending down from the left upper lobe. It is probable that these aneurysms were unconnected with the subacute bacterial infection of the ductus as aneurysms of the pulmonary artery have been described before in association with a simple patent ductus. The lamination and absence of bacteria in the contained thrombi suggest they were not formed as the direct result of infection.

The clinical response to ligation of the ductus—immediate reduction in bacteriæmia and later temporary sterility of the blood, with marked diminution in fever—strongly suggest that the ductus or adjacent part of the pulmonary artery was the main site of bacterial vegetations at the time of operation, and it is most disappointing that the post-mortem examination did not show in what way the vegetations had been destroyed.

It is, of course, obvious that death was due to infection of the mitral and aortic valves, evidence of which was entirely lacking before operation.

results in the cure of subacute bacterial infection complicating a patent ductus.

It is obvious that the original theory on the basis of which the first case was treated surgically does not explain why many of these patients have recovered following ligation, for the ligatures cannot possibly have been placed sufficiently far apart to include all the vegetations between them. In addition, this theory could not account for the remarkable reduction in fever lasting a month which occurred in the child (*Case* 4) who ultimately succumbed following recanalization of the ductus and in whom an enormous vegetation was found in the pulmonary artery at autopsy, presuming that at least part of this thrombus was present at operation eight weeks before death. Further, in *Case* 3, dark discoloration of the wall of the left branch of the pulmonary artery, which

Table I.—SUMMARY OF NINE CASES TREATED BY LIGATION

Case No.	Age	Sex	Apparent Cause of Infection	Diastolic Pressure		Infecting Organism	Post-operative Embolism	Residual Cardiac Murmurs	Result
				Pre-operative	Post-operative				
1	23	M.	?	60	80	Atypical *H. influenzæ*	None	Short systolic	Well (4 yr. 5 mth.)
2	19	F.	?	40	74	*Str. viridans*	None	Systolic and diastolic	Well (3 yr. 8 mth.)
3	17	F.	Dental extraction	58	76	*Str. viridans*	Pulmonary (7th day)	Faint systolic	Well (2 yr. 6 mth.)
4	10	F.	?	56	82	*Str. viridans*	Pulmonary (repeated)	Faint systolic. Diastolic later	Died (8 wk.)
5	29	F.	?	58	88	*Str. viridans*	None	Systolic	Well (2 yr. 4 mth.)
6	22	F.	Dental extraction	50	80	*Str. viridans*	Pulmonary (5th day)	None	Well (2 yr. 2 mth.)
7	26	M.	?	60	86	*Str. viridans*	—	—	Died ($\frac{3}{4}$ hr.)
8	33	M.	Circumcision	54	76	Staphylococcus, *Str. viridans*, Gram—ve bacillus	Pulmonary (during 1st wk.)	Faint systolic	Well (1 yr. 3 mth.)
9	15	F.	?	55	78	*Str. viridans*	Pulmonary (1st wk.). Repeated systemic (later)	Faint systolic. Aortic diastolic (later)*	Died (4 mth.)

* The patient's doctor now (May, 1944) reports that the 'humming-top' murmur has returned.

RATIONALE OF LIGATION IN THE PRESENCE OF INFECTION

Before discussing this difficult problem, it should be made clear that the recovery rate in this series (66 per cent) is approximately the same as that obtained by other surgeons. In the United States more than 30 infected cases have been treated by ligation and a large proportion of these have got well (Shapiro, 1943). (This includes 12 cases operated on by Touroff (1943), of which 10 survived operation and 7 recovered completely.) In this country Sellors (1943), Price Thomas (1943), and others have been equally successful. We may therefore take it as an established fact that ligation very frequently

felt firm, almost certainly marked the position of vegetations and yet this patient got completely well.

Boldero and Bedford (1924), commenting on the rarity of subacute bacterial endocarditis on the right side of the heart unless there was a leak into it from the left side, suggested that this might be due to venous blood being inimical to the growth of bacteria. If this suggestion were true, a ready explanation for the success of ligation would be available, for, if this were done at a stage when the vegetations were limited to the pulmonary side, the bacteria would be deprived of the arterial stream coming through this channel and might therefore be expected to die. It would further explain the observation (Touroff, 1943)

that those cases showing pre-operative systemic embolism, which is evidence of extension to the aortic opening of the ductus or to the aortic or mitral valves, rarely if ever, recover. (In this connexion, in our present state of knowledge, I would not subscribe to the view that such evidence is a contra-indication to operation. It is also worth noting that embolic nephritis and perhaps even cutaneous petechiæ may not necessarily indicate such extension, as *small* emboli can clearly pass through the pulmonary capillary bed, *vide Case* 1 which recovered.) However, there is no bacteriological evidence to support this thesis and, even if there were, the extremely rapid removal of bacteria from the blood-stream following ligation, demonstrated in *Cases* 6 and 9 and possibly *Case* 8, seems too quick a process to make this explanation likely.

Touroff (1942, a) has described in detail a theory which supposes that the cessation of the rapid stream through the ductus results in much diminished fragmentation of the infected clot, and that the lung capillaries, now less dilated and fed by an arterial stream no longer raised in pressure or volume, are able to filter off the few emboli which are formed. This hypothesis depends on several factors which require consideration :—

1. It assumes that the bacteria already circulating in the blood are very rapidly destroyed or removed from it. This would be expected in view of the experimental demonstration that organisms injected intravenously disappear with extreme rapidity from mammalian blood provided the source of supply is not continued (Reichell, 1939).

2. The theory pictures diminished fragmentation of the thrombus as a result of exposure to a less forceful blood-stream. This is reasonable, but obviously cannot be supported by experimental evidence.

3. It accords to the lungs an ability to act as a bacterial filter. The ability of the pulmonary capillaries to perform such a function receives support from Touroff's (1942, b) discovery of far fewer bacteria in a sample of aortic blood compared with one taken from the pulmonary artery at the time of operation, but before ligation of the ductus.

4. It presumes that the static thrombus heals by a process of organization. This is reasonable pathology, support for which was sought at the autopsy in *Case* 9, but unfortunately there was no clue as to the original site of the vegetations : the floor of the depression found in the pulmonary artery and representing the pulmonary end of the ductus was formed of well-organized fibrous tissue, but there appears no justification for assuming that this resulted from organization of vegetations.

To summarize, we do not yet know why most of these patients have got well, but Touroff's theory seems the most reasonable yet advanced. Cases treated by ligation in the future should be studied most carefully in order to discover the true explanation, for it is possible that this might have some bearing on treatment of subacute bacterial endocarditis involving other abnormalities.

SUMMARY

The anatomy, physiology, and pathology of the ductus arteriosus are briefly reviewed.

Nine cases of subacute bacterial endarteritis complicating a patent ductus and treated by ligation are described ; 6 of these patients are well to-day, from fifteen months to over four years after operation.

The technique of the operation is described.

The reason why ligation frequently results in cure of the infection is discussed.

CONCLUSION

The effect of ligation on infection of a patent ductus has been dramatic, although perhaps unexpected, and infection must now be considered an absolute and urgent indication for operation. Under these circumstances it is important that the supervention of infection should be diagnosed early ; any patient with a patent ductus who runs an unexplained fever for more than two weeks should be suspected of this complication.

It is difficult to pay proper tribute to all who have helped in this work for it represents a ' combined operation ' rather than the effort of a single individual. I would like to thank the physicians who referred the cases for operation : Dr. K. D. Keele, Sir Thomas Lewis, Dr. A. E. Gow, Dr. H. V. Morlock, Dr. Ronald Jones, Dr. E. F. Scowen and, in particular, Dr. Geoffrey Bourne, who has given me invaluable advice with all the cases. Dr. R. H. A. Swain gave much time and took infinite pains with the bacteriological investigations, and Professor L. P. Garrod gave his expert help when military service called Dr. Swain away. It would be ungrateful if I did not also acknowledge the very important part played by first-rate nursing care—especially that of Sister Piper.

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WAR SURGERY IN THE ROYAL AIR FORCE

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THIS paper is an attempt to place on record the surgical activities of the Royal Air Force during the four years of war. The objects of surgical services in war as in peace are the same: to save life, to limit morbidity, and to restore function. Yet in the field of surgical endeavour war always leads to great advances made in rapid strides. Each of the three Services has its own special problems. The dominating problem in the Royal Air Force is the care of air-crews. These carefully selected and highly trained young men are fighting either alone, as in the case of fighter pilots, or in small units of a few men forming that unique partnership—an air-crew. These men live and work in exceptional conditions; they are submitted to the special risks of flying at high speeds, to the hazards of weather, altitude, and cold, and, in addition, to the perils of exposure to the dangers from enemy action common to all Services. The air-crews are outnumbered many times by the ground personnel consisting of trained technicians: fitters, riggers, mechanics, engineers, armourers, electricians, instrument repairers, as well as equipment and medical personnel, all exposed directly, although to a lesser degree, to risks attributable to war. Both air-crews and ground staff and every member of the ancillary branches of the Service are liable to incidental surgical diseases and injuries which hamper the war effort. There are, therefore, problems special to the Royal Air Force and others common to all. What are these problems and what is the organization dealing with them? What facilities does the Royal Air Force provide, and what degree of success has been achieved?

THE SPECIAL PROBLEMS

Fatal Injuries.—In certain circumstances loss of life results from the multiplicity of injuries. In no other Service, and in no other conditions is this such a clear-cut and oft-repeated event: mid-air collisions, diving into the ground or sea at tremendous velocity, fierce and rapid conflagrations where petrol, cooling mixture, ammunition, and high explosives transform the aircraft into a vast blazing furnace. These accidents result in injuries which allow of no survival.

Analysis of these cases shows that they fall into three groups: The first results in a pulverization of the whole body; uncontrolled power-diving where the impact is extremely severe results in a disintegration of the body into small particles, the recognizable anatomical parts being no bigger than the head of the femur, or a portion of a finger, a toe, or a vertebra. The second group is more common and results in multiple injuries and fractures. Thus, a very recent mid-air collision of two four-engined aircraft returning at night from a successful operational sortie, resulted in thirteen deaths; examination revealed that, in only two were the fractures compound; in the others, although the skin was intact, showing bruising only, most of the bones were fractured, as many as twenty fractures being detected; the scalp may be intact and yet all the bones of the vertex and of the base are splintered into small fragments. Visceral injuries in such cases are severe and extensive; injuries to the heart, lungs, and main vessels are common; death is instantaneous in all but the very few cases that survive a few hours only. The third group of cases comprises burns so extensive as to result in partial or complete incineration. All these cases are fatal and death is instantaneous. It is at present difficult to visualize any preventive measures likely to diminish the incidence of such disasters.

Common Non-fatal Injuries.—Of the large number of war injuries those most commonly met with in flying personnel and of special interest to the Air Force surgeon are selected for more detailed consideration: Burns, wounds, frost-bite, immersion injuries, and head injuries. Fractures are not dealt with in this review except in the section on the General Organization of the Surgical Services.

BURNS

Burns account for an important number of R.A.F. casualties among air-crews. At the time of the Battle of Britain, most surgeons had but little experience of this type of injury, only a few took a special interest in them, and tannic acid loomed very large in the treatment. The burns

at the time of the Dunkirk evacuation provided experience of the immediate treatment and subsequently showed the sequelæ thereof. It is, however, from the time of the Battle of Britain that great interest was aroused in this subject, resulting in the formation of Special Burn Centres within the R.A.F. medical organization. The complex problems, both of pathology and of treatment, have stimulated interest, and rapid progress has been made in the management of these cases.

Accurate observation of early and late effects of burns has led to variations and improvement in the technique and in the principles underlying the rationale of the treatment. Strict adherence to the narrow path of accepted methods was quickly abandoned in favour of open-minded observation of the effects of different therapeutic measures.

The special problem of the burned R.A.F. crews is in the majority of cases that of second-degree and third-degree burns of the face and hands. Burns of the trunk or of the lower extremities differ not at all from those seen in other services or met with among civilian casualties.

Before discussing methods of treatment, attention must be drawn to certain features of clinical and pathological importance :—

1. In R.A.F. crews the survivors belong to a group where the area of the burn is relatively small, the part affected localized to the hands and face, the degree of burn second or third. Therefore, *mortality* in this type is small, but *morbidity* is great.

2. There is real difficulty in distinguishing soon after the infliction of the injury, second-degree from mild third-degree burns. There is, of course, no difficulty at either end of the scale, but in the borderline between partial and total skin loss even the most experienced cannot with certainty establish an accurate diagnosis. James Dingwall, of the Cornell University, recently described a method of distinguishing second-degree from third-degree burns. It consists in the intravenous injection of 10 c.c. of a 20 per cent solution of fluorescein. Within fifteen seconds from the time of injection the burned area when examined under ultra-violet light is said to appear yellow or yellow-green if only of second degree, and black if of third degree. This test merits further investigation.

3. The immediate response of the tissues to thermal injuries is *œdema*. It is very marked, of rapid onset, and progressive; it affects vitally the choice of the immediate and subsequent treatment. It is the most important clinical manifestation and it has been shown experimentally that burns result in an immediate and marked increase of lymph-flow. Similarly, inhalation of flame results in œdema of the glottis, larynx, and trachea.

4. For a considerable time the blister fluid remains sterile—a fact to be remembered, especially in the first-aid treatment. Nevertheless, as pointed out by Colebrook and others, blister fluid is an excellent culture medium and organisms present in the deeper layers of the skin may here find a favourable medium and so lead to delayed infection. The decision as to how best to deal with the blisters requires experience, but in first aid they are a self-provided dressing hardly to be improved on.

5. The degree of shock does not always correspond to the surface extent of the burn; and associated injuries when present complicate the clinical picture.

Keeping these few points in mind, certain principles of treatment become apparent. All treatment falls into three stages; the immediate or first-aid treatment; the treatment during the period of healing; the restoration of function.

Immediate Treatment.—In the aircraft, on the field, or even in the station sick quarters, it is well to remember that wrapping up the burn and leaving it alone may be best, as it does not compromise subsequent treatment. Clothing should be removed only if soaked in petrol or cooling-mixture; warmth, oxygen, morphia, and administration of plasma are the cardinal points in the treatment. On the exposed parts, vaseline or antiburn jelly (3 per cent sulphonamide in a water-soluble base) provided in the first-aid equipment is applied.

The Stannard Glove.—The Stannard silk envelope designed by Bunyan, made of transparent waterproof silk fabric, can be used either as a first-aid measure or in subsequent treatment. In the form of a glove it is now carried by every member of an air-crew and is enclosed in a small first-aid pack (*Figs.* 11, 12). Each glove contains a weighed amount of one of the sulphonamide compounds (7·5 g. of insoluble sulphacetamide). It can be easily applied by the injured man himself and is retained in position by adhesive tape.

Subsequent Treatment.—There are two main principles of treatment: the closed method and the open method.

The *closed method*, be it by tannic acid, one of the dyes, or a combination of coagulants, has merits in second-degree burns, in extensive burns of the trunk, the upper arm, or the thighs; it may be a life-saving measure and as such should be employed regardless of subsequent complications—a live patient with a septic burn being at all times preferable to a corpse. The closed method, however, should have no place in the treatment of burns of the face, hands, genitalia, and perineum.

The *open method*—or treatment by vaseline gauze, tulle gras, saline packs, C.T.A.B. in lannette wax, with local application of sulphonamides—has many advantages; but experience has shown that frequent dressings are badly tolerated in the early stages and the individual needs of each patient dictate the technique of the open method in each case. Colebrook's antiseptic dressing is a cream of the following

composition : sulphanilamide 3 per cent, sulphathiazole 3 per cent, glycerin 10 per cent, castor oil 27 per cent, lannette wax 12·3 per cent, and

The First Dressing in Hospital.—The importance of the first dressing in hospital can hardly be exaggerated. Cleansing of the burn must be

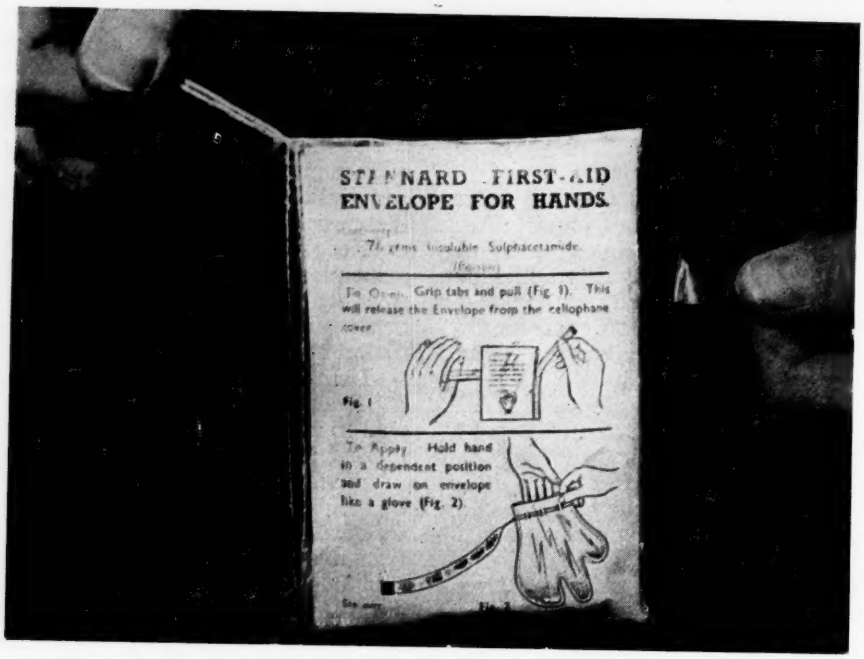
ENVELOPE FOR HANDS
To Open. Grip tabs and pull (Fig. 1). This will release the Envelope from the cellophane cover.
Fig. 1
To Apply. Hold hand in a dependent position and draw on envelope like a glove (Fig. 2).

FIG. 11.—Packet containing first-aid envelope for hands. Instructions for opening the packet and for the application of the glove are printed on the cover.

FIG. 12.—First-aid Stannard sulphonamide glove. It enables the air-crew casualty to use his hand.

water. This cream can be left untouched for seven, ten, or even twelve days. It is admirable for non-infected burns, and as a first dressing. The object of treatment at this stage is to obtain epithelization or to prepare a surface suitable for grafting. The earlier the grafting the less the deformity and functional disability.

gentle ; no scrubbing, no ether soap, no trimming or débridement except of tissues already dead and loose ; blisters should not always be opened as a routine, but only if extensive, and above all no anæsthetics except morphia should be used unless associated injuries make this unavoidable. Dressings can and should be done in bed and

only exceptionally, in the presence of other injuries, is the patient taken to the operating theatre.

Subsequent Dressings.—These are more tedious and elaborate. In R.A.F. Burn Centres the provision of constant-temperature saline baths has facilitated the treatment at this stage. Dressings are removed painlessly or are floated off in the bath, discharges are washed away, movements of joints encouraged. At this stage of established infection routine daily dressing with sulphonamide powder (10 per cent) and vaseline gauze is the method of choice; but cases where no response to sulphonamides is obtained in a short time become sulphonamide resistant. It is here that propamidine has proved of value. But the most remarkable results have been obtained with penicillin. Flight-Lieutenant Bodenham recommends its use in the form of cream or powder in the strength of 100 units per gramme. Daily applications are necessary and lead to an early elimination of coccal infection. Success or failure in obtaining a clean granulating surface or complete healing depend primarily on factors intrinsic to the lesion—its depth, its extent, and degree of contamination—but it also depends in no small measure on such imponderable factors as the interest and enthusiasm of a young medical officer, the competence and dexterity of orderlies, and the quality of nursing. Training of orderlies, nurses, and doctors has provided the R.A.F. Burn Centres with organized team-work essential in the treatment of these lesions. The ideal team consists of a surgeon, pathologist, biochemist, physician, and a specially trained nurse and orderly.

Treatment of Burned Hands.—Severe burns result in contractures, the typical one being loss of flexion at the metacarpo-phalangeal joints, loss of extension at the interphalangeal joints, or, worse still, hyperextension at the metacarpo-phalangeal joints—the so-called 'frozen hand', leading to the claw-hand (*Fig.* 13). It is therefore of the utmost importance to preserve the position of function, called by Flight-Lieutenant Bodenham the 'basic position', throughout the period of healing and for a time after epithelization is complete. Œdema is reduced by elevation of the hands and the following position of choice adopted: dorsiflexion at the wrist, mid-flexion of fingers at all joints, and apposition of the thumb. Light aluminium splints lined with piano felt, made specially for each hand and for each individual patient, are used to maintain the position of choice; flexion or extension is obtained by elastic or whalebone, or a light metal spring attached to the splint and by a leather strap to the finger. Movements are encouraged and facilitated by immersion in baths. The patient is educated to appreciate the importance of movements and is taught the six essential movements: flexion, extension, and apposition of fingers, flexion of metacarpophalangeal and distal joints, and abduction of fingers. Plaster immobilization is justifiable only in exceptional circumstances and then only for a short period.

Skin-grafting.—This should be done at the earliest possible moment; and only by a surgeon adequately trained and conversant with every detail of the special technique. Time is often saved by grafting a raw surface which *looks* clean although bacteriologically still infected. Grafts must be on a generous scale; small grafts of the eyelids, for instance, will not remedy an ectropion and inadequate grafts on the hands will not prevent serious disability, although there is no raw surface.

FIG. 13.—Claw-hand—the end-result of uncontrolled contraction following burns. The metacarpophalangeal joints are in extension, all other finger-joints are flexed, the thumb is in opposition. Such a hand is functionally useless. (Flight-Lieutenant Bodenham.)

Reduced to its simplest terms, the treatment of burns aims at prevention of sepsis, rapid healing, correction of deformities, and restoration of function. No single method of treatment is a panacea for all cases of burns, but that skilled team work, adequate facilities, and an open mind can rescue the majority of cases and return them to a near-normal life has been abundantly shown by the number of air-crews who have returned to flying duties, including operational flying.

WAR WOUNDS

The outstanding points in the treatment of wounds in the present war can be summarized under the four following headings: (1) The use of blood or its derivatives in the treatment of shock; (2) The control of bacterial infection by chemical means; (3) Conservatism in the actual surgical procedure; (4) The systematic use of plaster-of-Paris not only in the immobilization of fractures but in the fixation of dressings for soft-tissue injuries. As a result, the mortality among those who reach hospital has been reduced to an average of 2·5 per cent and the return to duty is estimated at 75 per cent. It is admitted that the degree of success is inversely proportional to the time between the infliction of a

wound and adequate treatment; this all-important time factor is one of the favourable circumstances in the Royal Air Force. Thus, in Bomber Command operating from Great Britain, the longest sortie does not exceed nine to ten hours, and presuming that the injury occurs over the target, a little more than four and a half to five hours will elapse before aid is reached. Those wounded on the ground in Air Force Stations are within immediate reach of the Station Medical Officer. Moreover, station sick quarters, mobile field hospitals, and R.A.F. hospitals are not, as a rule, called upon to deal at any one time with large numbers of casualties, and so the period of waiting is further reduced. These favourable conditions have dictated the policy of collecting air-crew casualties into R.A.F. hospitals at the earliest possible moment, and, consequently, there is greater clinical control of the case throughout the entire period of incapacity from operation to full rehabilitation and more rapid recovery and an early return to duty are achieved.

To illustrate the principles of the surgical treatment of war wounds, the type of injury met with, and the results of treatment, the following illustrative cases have been selected. War wounds due to enemy action, as met with in the R.A.F., can be divided into the following types: multiple foreign bodies, flak injuries, machine-gun bullets, hand grenades, and bomb explosions. The wounds differ in type according to the missiles.

Multiple Foreign Bodies.—

Case 1.—Pilot Officer, aged 20. Shot down in France in June, 1940. Multiple small wounds of the back of the neck from fragments of armour plating sheered off the Hurricane cockpit by cannon shell. First-aid treatment, antitetanic serum, and antishock treatment was given and he was transferred to England within forty-eight hours. Removal only of some of the more superficial foreign bodies was carried out. Rapid recovery and return to duty.

Case 2.—Group Captain, aged 42, commanding a Fighter Station in the vicinity of London. Wounded in action in November, 1940. Landed uneventfully at his own station. Multiple small wounds in the back. Transferred to an R.A.F. hospital within two hours. Explored, foreign bodies extracted, wound sprayed with sulphonamide and lightly packed with gauze. Healed in two months. Returned to duty.

Case 3.—Air Gunner, aged 20. Wounded in action in June, 1940. Admitted to an R.A.F. hospital the same day. Compound comminuted fracture of right forearm with numerous small metal foreign bodies. No injury to nerves or main vessels. Trimming of wound, no attempt at removal of foreign bodies; sulphonamide powder, vaseline gauze, and plaster. Returned to full duties as air gunner in six months.

Flak Injuries.—

Case 4.—Air Gunner, aged 25. In November, 1941, over Bremen, wounded by flak in left pectoral area. First-aid dressing applied in the aircraft; morphia refused. Very considerable loss of blood. Returned to home station and admitted to station sick quarters. Ragged wound over left pectoral muscles and axilla. Resuscitation: morphia, heat, transfusion of 4 pints of stored blood. Transferred to an R.A.F. hospital within twelve hours and operated on by Wing Commander G. Morley: Wound toilet, removal of large foreign body; sulphonamide, vaseline gauze, and plaster. Plaster changed in fourteen days and again three weeks later, when the wound was healed. An arteriovenous aneurysm of the third part of left axillary artery was noticed within three months. Following manual compression of five minutes three times daily for four months, I excised the aneurysm. Uneventful recovery. Returned to operational flying ten months later.

Case 5.—Sergeant, aged 22. Sustained a head injury from flak on return from Essen in June, 1943. Two pieces of metal perforated the left eye, travelled across the nasopharynx, and came to rest on the right side at the level of the angle of the jaw near the carotid. No attempt was made to remove them. A third piece hit the left parietal bone, perforated both outer and inner tables, and exposed the dura mater. The parietal wound was excised, the foreign body removed, the wound sprayed with sulphonamide and sutured. Subsequently the left eye socket was reconstructed and an artificial eye fitted. He has returned to duty in less than three months.

Machine-gun Bullets.—

Case 6.—Aircraftman, aged 27. While uncoiling a belt of ammunition, one end struck the ground and one bullet exploded, entering the orbit. The nose of the bullet hit the supra-orbital ridge and was deflected downwards along the upper orbital margin. He was admitted to a civilian hospital, given first-aid and transferred forthwith to an R.A.F. hospital. The orbital tissues were explored and the bullet removed. The eye was not damaged and there is full recovery of binocular vision.

Cannon Shell.—

Case 7.—Sergeant Air Gunner, aged 23. Hit by cannon shell from a night fighter when returning from a raid on Essen. The shell hit the right foot, causing severe pain and loss of consciousness. First-aid dressing applied in the aircraft. Transferred to nearest civilian hospital as soon as the aircraft landed. The wound was cleaned and the foot put in plaster. Two days later transferred to an R.A.F. hospital. On removal of the plaster an extensive wound was found, involving the sole and outer side of the foot (*Fig.* 14, A). The fourth and fifth toes were gangrenous and were hanging loose, together with the tendons and metatarsal bones. The dead tissue was cut away, sulphonamide applied, and the foot put in plaster. On removing the plaster two weeks later, it was found that the wound was still dirty, but the skin over the heel and the weight-bearing part of the foot were intact (*Fig.* 14, B). Saline baths were instituted and sulphonamide powder applied. Within three weeks the wound was clean and a free skin-graft applied. The wound healed (*Fig.* 14, C) and the patient has no functional disability.

Case 8.—American Sergeant, aged 19. Sustained a cannon-shell wound of the chest in a daylight raid on Paris in April, 1943; admitted three hours later to an R.A.F. hospital in England, in extremely shocked condition from severe loss of blood. The co-pilot, a medical student, applied sulphonamide to the wound and dressed it. X-ray examination revealed a non-exploded cannon shell beneath the right clavicle. The lung fields were clear and the heart shadow was not displaced. There was a large ragged wound,

2 in. × 4 in. over the upper part of the sternum; the wound was bleeding profusely. The inner half of sternomastoid muscle was torn and a portion of it was missing. He was operated on by Squadron-Leader

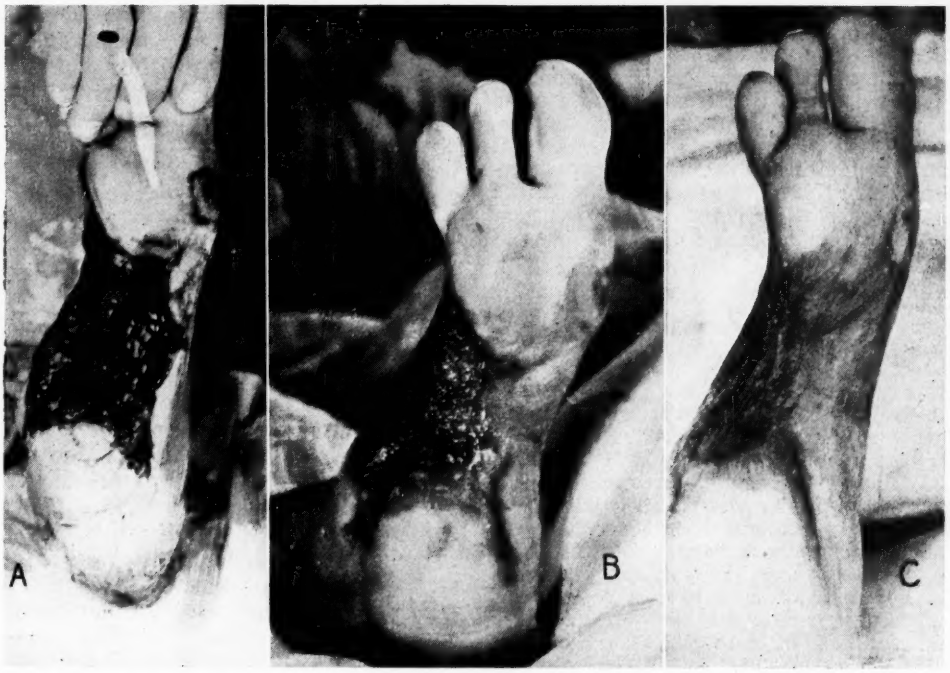

FIG. 14.—Cannon-shell wound of foot. A, 2 days after injury; B, 14 days later before grafting; C, 1 month after grafting. (Squadron-Leader D. N. Matthews.)

FIG. 15.—Hand-grenade wounds. A, Immediately after explosion; B, 2 weeks later, before grafting; C 1 week after grafting; D 42 days after injury.

the clavicle had been blown away and most of the manubrium sterni was missing, revealing the great vessels and upper part of the pericardium. The D. N. Matthews. Hæmorrhage was controlled by gauze packing and a 5-pint transfusion of stored blood given. The unexploded cannon shell was removed

under local anæsthesia and handed to the Bomb Disposal personnel. It was noticed that a hiss of air escaped as soon as the tissues overlying the shell were cut. The patient remained unconscious during the next ten days and had to be fed by a nasal tube. There was a severe bruise over the occiput, which probably accounted for the cerebral contusion. Each time the pack was removed from the sternal wound for the application of sulphonamide powder, brisk hæmorrhage recurred. On the tenth day, under a general anæsthetic, the wound in the neck and chest was explored by Mr. Tudor Edwards; a tear was found in the internal jugular vein at its junction with the right subclavian. A portion of the jugular was removed and the ends ligatured. The wound healed satisfactorily. He was repatriated to America in a plaster spica.

Hand Grenade.—

Case 9.—Flight Lieutenant. This officer was demonstrating the mechanism of a hand grenade when it exploded, inflicting an extensive lacerated wound on the dorsum and palm of the hand (*Fig.* 15, A). Four hours later the wound was trimmed, cleaned, dusted with sulphonamide powder, covered with vaseline gauze, and put in plaster. The hand was elevated for the next fortnight, the plaster was then removed, and a clean granulating surface found (*Fig.* 15, B). Immediate grafting was done by means of a sheet of Thiersch graft cut into small squares and placed $\frac{1}{8}$ in. apart; a fresh plaster was applied. This was changed at the end of one week, when the grafts were found to have taken, their edges coalescing (*Fig.* 15, C).

Bomb Explosions.—

Case 10.—Group Captain, aged 29. This officer, commanding a Bomber Station, was running towards an aircraft which had crashed on taking off with a 4000-lb. bomb aboard. Knocked down by the blast of the explosion, he was hit by a large fragment which nearly severed the right arm below the shoulder, another fragment caused a perforating wound of the knee-joint. First aid and resuscitation were given at the station sick quarters; the transfusion was continued in the ambulance during the transfer to an R.A.F. hospital. The right arm was amputated; the wound in the knee cleaned, trimmed, and sprayed with sulphonamide; the leg was put in plaster. This officer returned to duty three and a half months later and has since rendered distinguished services as officer in charge of a 'clutch' of operational bomber stations.

General Principles of Treatment.—The above 10 cases illustrate the types of war wounds inflicted by different missiles as seen in R.A.F. casualties. The principles underlying treatment can be summarized as follows:—

Resuscitation is of paramount importance. It takes precedence over treatment of wounds, with the exception of control of hæmorrhage. Warmth, sedatives, oxygen, and fluids require no emphasis. Often these remedies alone suffice; but pronounced or severe states of shock invariably require in addition intravenous medication with blood or plasma. In burns in particular, plasma is the fluid of choice as the hæmo-concentration is a contra-indication to the administration of whole blood. In shock resulting from or concomitant with hæmorrhage, fresh blood or stored blood is indicated. The total amount needed and the rate of administration vary with the injuries sustained, the degree of shock, and the time elapsed since infliction of the wound. One or two pints may suffice to raise the blood-pressure to 110 mm. Hg or more, but if need be 4 to 6 pints can be given, the amount being controlled by the blood-pressure readings and general clinical observation. Resuscitation has achieved its object when the injured is fit for operation. No time should be lost in performing the necessary operative procedures as otherwise secondary shock may occur.

Chemotherapy.—The control of bacterial infection by chemotherapy is so great an achievement as to overshadow almost all medical advances in recent years. Systemic chemotherapy is well established in many conditions, both medical and surgical. The more recent advances concern the local antiseptic treatment of wounds. The success of local application is due to the great concentration of the drug. Of the three compounds most commonly used—sulphanilamide, sulphapyridine, and sulphathiazole—the latter combines the highest dissolved concentration with persistence of effect. The greatest value of the local application of sulphonamides is the *prevention* of infection. To overcome established infection, when treatment by sulphonamides has failed, two other chemical substances have been used with some success—proflavin in powder form, not in solution, and propamidine in a water-soluble base. Both substances have proved successful in some cases of wounds and burns when sulphonamides have failed; but the most remarkable substance of recent application is penicillin, which has been appropriately termed a 'biological antiseptic'. It was first used in the R.A.F. in June, 1942, in a case of severe staphylococcal septicæmia following osteomyelitis with a dramatic recovery of an apparently hopeless case. It has successfully controlled staphylococcal septicæmia, possibly the only substance so far to do so; it succeeds where sulphonamides fail. It can be used locally or systemically—it promises to open a new era in the control of infections. Much work in many fields is yet needed to establish the relative merits of these various substances, but this much is certain—that prevention of wound infection is possible and chronic suppuration of wounds is by no means inevitable.

Penicillin is likely to alter the established principles of the treatment of war wounds. Whereas with sulphonamides it is a cardinal principle that war wounds must not be primarily sutured, with penicillin closure of the wound, even when infected, is permissible and sometimes essential. Healing of such wounds is clearly an indication that penicillin is likely to alter our conception of what are sound surgical principles.

The Surgical Treatment of Wounds.—Adequate surgical treatment of wounds remains the most important part of the treatment. The use of sulphonamides and of penicillin does not replace it; it does,

however, influence the technique of the treatment. The surgeon dealing with a war wound should appreciate the difference between such wounds—which are almost bound to become infected—and wounds seen in peace-time. The actual method of dealing with the wound depends upon the time elapsed since its infliction. Up to eighteen hours—at most twenty-four hours—a wound may be contaminated only; beyond that limit of time it should be considered as infected. All wounds are in need of an initial surgical toilet; in the early stage, *excision* of the wound may be possible and advisable, later on it is still possible, but no longer desirable, and the surgeon must guard against surgical intervention lapsing into surgical interference. When the time for excision has been passed, there is still time for *débridement*; later still trimming, drainage, and counter-drainage only may be permissible. Excision, débridement, or trimming must always be purposeful, adequate, and gentle; only dead, loose, dirty tissue should be excised; vessels and nerves must be respected; the skin spared as much as possible; foreign bodies—missiles, clothing, and loose pieces of bone—should be removed. Adequate exposure of the whole wound is essential and this should be achieved by enlarging the wound in its long axis and exploring all the planes of tissue involved. Of all the tissues, muscle should be excised most adequately. *Primary suture of war wounds should never be done unless penicillin is available.* If the wound remains clean, secondary suture within four or five days can be carried out.

Dressing of the Wound: Hæmostasis having been achieved, the wound is powdered or rather 'frosted' over with sulphonamide. The dressing of choice is vaseline gauze; this is neutral to sulphonamide, non-irritating to the tissues, permits drainage, and protects the surrounding skin. This dressing is kept in position by two slabs of plaster or a complete plaster cast which should include the joints proximal and distal to the wound, so ensuring complete immobilization.

Indications for Amputation: Only when survival of a limb is out of the question owing to injury to the main vessels or in the presence of established gangrene, is primary amputation indicated. Every effort to save a limb is worth while, but judgement and experience are needed not to attempt to do so at the risk of losing the patient. Amputation stumps in war wounds should be treated as wounds and no primary suture attempted. Conservatism in the matter of amputation was dictated in the R.A.F. by the frequency of multiple severe injuries. When two limbs or sometimes three are the seat of severe trauma, amputation is not unnaturally postponed. The fact that R.A.F. casualties reach R.A.F. hospitals *early* has no doubt contributed towards this conservatism, which in the end showed some remarkable recoveries.

The cardinal principles of surgery of war wounds can be summarized in four words: resuscitation, débridement, chemotherapy, immobilization; and the surgeon who deals with war wounds should constantly remember that to achieve success he should: excise—conservatively; drain—adequately; immobilize—completely; and rehabilitate—early.

FROST-BITE

The problem of frost-bite as affecting the flying personnel of the R.A.F. has been solved in practice by preventive measures. Frost-bite conditions exist at a temperature of − 20° C. and below. The fall of temperature in relation to altitude is computed to be approximately 1° C. for every 500 ft.; it is therefore possible to estimate the probable temperature likely to be encountered at any given altitude. The crews of Bomber Command operating from Great Britain are submitted to frost-bite conditions throughout the whole year, and for a period of seven or eight months extremely low temperatures are met. The problem was therefore of considerable practical importance, as the victims of frost-bite were lost to operational duties for various periods of time and sometimes altogether.

Clinical Considerations.—Frost-bite affects the hands and fingers, the feet and toes, the face, or a combination of sites. It not infrequently results from touching metal parts with bare hands. According to the degree of injury the lesions can be subdivided into three groups: slight, moderate, and severe. The *slight* cases are those where the numbness, anæsthesia, and pallor or greyness of skin regress with only slight shedding of the most superficial layers of the skin; at this stage the damage is still a reversible reaction, death of tissue has not occurred; about 30 per cent of cases classified officially as frost-bite fall into this group. In the *moderate* degree, blistering follows within a period of twelve hours or more (*Figs.* 16, 17), but the capillaries and arterioles respond to treatment, circulation is restored, and only little of the superficial tissue is lost; this group accounts for 45 per cent of cases. Seventy-five per cent of all cases of frost-bite in air-crews are therefore mild and recover rapidly. The remaining 25 per cent of cases are *severe* and result in gangrene, aggravated by infection, with consequent loss of fingers or toes, prolonged periods of incapacity, permanent damage to the skin, severe hyperhidrosis, and trophic changes in the skin and nails. The conditions under which frost-bite occurs are illustrated, in the very brief histories of the following cases.

Slight Cases.—

Case 1.—Wireless Operator, aged 22. In December, 1939, flying at 23,000 ft., took off gloves to adjust wireless; on return noticed that the fingers were cold and anæsthetic. A few blisters formed the following day. Healed and returned to duty in twelve days.

Case 2.—Air Observer, aged 21. In December, 1940, flying at 17,000 ft. over North Sea; temperature — 32° C. He was wearing three pairs of gloves, silk, wool, and leather. Tips of most fingers became numb,

anæsthetic, and blue. Rapid recovery. Return to duty in fourteen days.

Case 3.—Wireless Operator–Air Gunner, aged 22. In January, 1942, flying at 17,000 ft., temperature — 32° C., handled a metal flash bomb for ten minutes. On return to Base, the right hand was bluish and the little finger was swollen; blisters developed the next day. Healed rapidly.

FIG. 16.—Frost-bite. Moderate degree. Œdema, early blistering, and hæmorrhage.

Moderate Cases.—

Case 4.—Second Pilot, aged 20. In November, 1940, was instructed to hold a flare in the chute until told to drop it. This resulted in the exposure of hands to the outside air for twenty minutes; temperature — 20° C. Two pairs of gloves worn. Moderate degree of frost-bite developed in all fingers; recovery in five weeks.

Case 5.—Air Gunner, aged 21. In rear-gunner's turret for four hours on the night of Jan. 21, 1942, mostly at 10,000 ft. Feet cold most of the time. On return noticed that the fingers were cold, white, and anæsthetic, and the toes bluish, swollen, and painful. Blisters developed within fourteen hours; eventually lost most of the nails. Recovered in three months.

Severe Cases.—

Case 6.—Air Gunner, aged 23. In December, 1939, was in the rear turret at 18,000 ft. for two hours. Took off gloves for half an hour to adjust guns. The fingers were numb, but he felt no pain and was not aware of the cold. Severe frost-bite, with loss of skin; raw surfaces healed in four months; mobility of fingers impaired.

Case 7.—Wireless Operator–Air Gunner, aged 21. In December, 1940, flying at 23,000 ft.; temperature — 50° C. Noticed coldness and numbness of fingers for one to two hours before descent. Frost-bite with

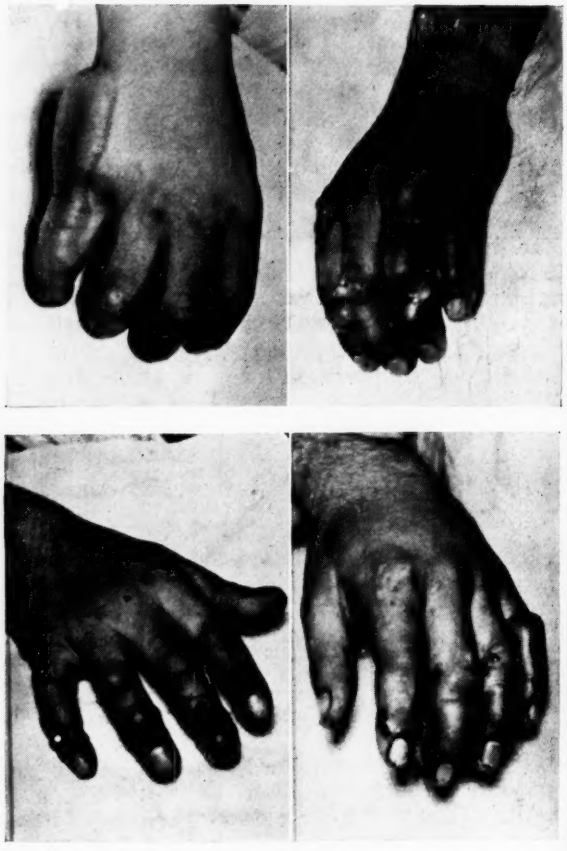

FIG. 17.—Same case as *Fig.* 16, 48 hours later. Marked increase in size of blisters and hæmorrhage in smaller blisters. This case made a good recovery.

subsequent loss of two fingers, and loss of nails and trophic changes of skin. Ten months off duty.

Case 8.—Air Gunner, aged 21. In October, 1941, during a six-hours' sortie, mostly at 18,000 ft., removed gauntlets several times to adjust helmet. Severe frost-bite developed, gangrene of terminal phalanges of two fingers and permanent disability from trophic changes and fixation of joints.

Causative Factors of Frost-bite in Air-crews.—A study of the various factors reveals that the most vulnerable member of the crew is the rear gunner, more than 53 per cent of cases of the series occurring in rear gunners; the next in frequency is the wireless operator and the other gunners. In most cases exposure of the hands was deliberate and thoughtless; mechanical failure of oxygen supply or of the heating accounts for some of the cases.

Incidence.—During the four years of war the incidence of frost-bite has greatly decreased. The decrease is not only relative to the number of personnel and sorties, but is absolute. In the latest period from October, 1942, to March, 1943, in the Bomber Command personnel operating from Great Britain, the incidence varied from 0·015 to 0·02 per cent, a truly negligible figure.

Prevention of Frost-bite in the R.A.F.—The remarkable reduction in incidence amounting to virtual abolition of frost-bite in air-crews was achieved gradually by preventive measures, education, and technical improvements. Heating of aircraft, provision of electrically heated clothes (gloves, stockings, and waistcoats), and improved oxygen equipment are the most important factors, but in addition education of air-crews by the Squadron Medical Officers, valeting of flying clothes, and testing of electrical connexions and oxygen apparatus on testing panels installed in the crew rooms have reduced to a minimum the preventible accidents.

Treatment.—A study of records shows that rapid progress was made in the methods of treatment. Rubbing with oil or turpentine soon gave place to painting with coagulating dyes; this, in turn, was replaced by sulphonamide powder and cotton-wool packs. The recent experience in the Royal Air Force supports the view that elevation of the limb, avoidance of trauma, and *cooling* of the affected parts leads to the minimal loss of tissue, absorption of blister fluid, and reduction of œdema. Cooling of the frost-bitten part can be achieved by means of ice packs, a stream of cold air from a fan, or iced saline packs, but, better still, by simple exposure to room temperature. It should be emphasized that recovery with trivial loss of tissue can only be achieved if the case is slight or moderate in degree and treatment given early. Gangrene and infection, once established, must be treated on general surgical principles.

IMMERSION INJURIES

These injuries result from exposure to sea water and the effects of cold. They occur in R.A.F. personnel, who, after 'ditching', remain for some time in a dinghy, and also as the result of torpedoing of ships. The general effects of exposure, the concomitant shock, and the degree of damage due to immersion depend mainly on the temperature of the water, the length of exposure, and to associated trauma. The feet, ankles, and legs are most commonly affected, but similar changes in the hands are well known. The main clinical features are swelling, numbness, tingling, loss of sensation, and desquamation. Impaired circulation is shown by bluish discoloration of the affected limbs; later erythema occurs, and this is accompanied by increased swelling and pain. The vascular changes show the cycle of vasoconstriction followed by vasodilatation. The painful stage occurs with the return of circulation and lasts a short time only. Blister formation is occasionally seen. The effects of exposure are aggravated by the incidental injuries such as bruising of the skin, sprains, and effusion of blood into muscles or joints. In cases rescued within six to twelve hours the recovery is rapid and no permanent disability results. In more severe cases neuritis, excessive sweating, trophic changes of the skin and nails, and persistent tenderness, especially of the soles of the feet and the palms of the hands, are the usual delayed effects. If the exposure is prolonged and the weather conditions bad, the circulatory changes may be so severe that gangrene of toes, fingers, feet, or hands may follow. There is clear evidence of the protective value of clothes, socks, flying boots, gumboots, etc. The mild cases recover in ten to fourteen days; the average stay in hospital is three to five weeks, but in severe cases return to duty is delayed for periods up to six months. Treatment is similar to that in cases of frost-bite. It consists in general measures to combat shock: elevation of the affected limbs, cooling by exposure to room temperature, and surgical cleanliness.

HEAD INJURIES

A study of head injuries sustained in flying by members of air-crews reveals some interesting points. During the first two years of the war, 1545 cases were recorded; and the available data were analysed. The cases were divided into five groups: (1) Multiple injuries and head injuries; (2) Head injuries only; (3) Maxillo-facial injuries; (4) Head and maxillo-facial injuries; (5) Head injuries with fracture of one or two other bones. This classification showed the following:—

1. That head injuries alone or in association with multiple injuries account for three-quarters of the cases (1116 fatal and non-fatal cases).
2. That maxillo-facial injuries are relatively few; 162 of the total of 1545 cases.
3. That the combination of head and maxillo-facial injuries was equally small, 166 of a total of 748 survivals.
4. That none of the maxillo-facial injuries proved fatal.

The end-results of cases of head injury can be expressed axiomatically by the law of 'all or nothing'; thus, *if a case of head injury escapes death, the injury is such that return to full flying duties can confidently be anticipated.* From the earliest days of the war, provision was made for the rapid segregation of air-crews suffering from head injuries, and their transfer to special centres dealing exclusively with head injuries or maxillo-facial cases. This ensured early and highly skilled specialized treatment, with the result that 74 per cent (553 cases) of survivors returned to a full flying category and the majority of these did so in a period of two months or less.

Type of Injury.—Head injuries fall into two main groups: (1) Fatal; (2) Non-fatal—about equal in number. These groups represent two

different clinical entities having no common denominator. Thus, most cases of *fracture* of the skull, especially in association with multiple injuries, resulted in death; of 820 cases of fracture of the skull only 55 cases, or 6·5 per cent, survived, whereas *all* the cases of concussion lived. The figures indicate that the kind of accident that leads to either a fracture of the skull with other injuries or a double fracture of the skull alone, is indeed almost invariably fatal; but a single and uncomplicated fracture gives a reasonable chance of recovery, for of 58 fractures of the vault 38 survived. The severity of injury is also shown by the fact that 83 per cent of the fatal cases die immediately, that is, they are dead when taken from the aircraft or when found. In contrast to the fatal head injury, the non-fatal group is characterized by the very small number of fractures of the skull, most cases coming under the heading of concussion, scalp wound, or maxillo-facial injuries.

The Fate of the Survivors.—The total number of survivors, 748 cases, were studied from the point of view of their return to flying duties and their degree of usefulness as members of an air-crew. The wastage of personnel amongst survivors from head injuries is surprisingly small and the return to a full flying category the rule rather than the exception. Of 748 survivors no less than 553, or 74 per cent, returned to full flying duties; this figure is the lowest limit, as 79 cases had not been determined at the time of the investigation, and some of these would normally return to flying.

The Rate of Recovery.—Most cases of head injuries usually recovered in less than two months. Scalp wounds, laceration of the face, and fractures of the nose show the quickest recovery. The return to duty following head injury after a comparatively short period of incapacity compares favourably with the end-results of other injuries.

ORGANIZATION OF SURGICAL SERVICES IN THE R.A.F.

The Surgical Services of the Royal Air Force aim at the provision of all specialized treatment within the R.A.F. and in a few selected civilian centres closely associated with its medical services. It embraces the whole field of treatment from the collection of casualties, the provision of first aid, the maintenance within the R.A.F. hospitals of specialized centres for those types of injuries requiring specialist treatment, to full rehabilitation and accurate assessment of the degree of fitness for flying at the termination of treatment and a complete follow-up system till a permanent flying category is reached.

Collection of Casualties.—Towards the latter part of the period of the Battle of Britain, the Air Ministry reached the decision that air-crew casualties in England and Wales should be collected and transferred into R.A.F. hospitals at the earliest possible moment. Experience during the subsequent three years fully justified the wisdom of this decision both as regards the individual casualties who received all their treatment under one authority, and as regards the Service as a whole, as it ensured the earliest return to flying duties and the best use of the personnel. To ensure a steady collection of air-crew casualties in the United Kingdom a system of notification was established. It embraced all possible locations of the casualties and the notification was sent by the quickest possible route to the Central Medical Establishment of the Royal Air Force. R.A.F. Medical Officers on becoming aware that an air-crew casualty had occurred, forwarded the notification indicating the location of the casualty, the nature and degree of injury, and whether sustained in flying, in action, or otherwise.

Arrangements were made with the Admiralty and the War Office for naval and military hospitals to notify the R.A.F. Central Medical Establishment of the admission of all air-crew casualties. Full co-operation of the Ministry of Health and of the Home Office was obtained and the admission of an air-crew casualty to a civilian hospital was notified through the local police to the nearest R.A.F. station, who, in turn, forwarded the information to the Central Medical Establishment.

The Casualty Collection Department of the Central Medical Establishment was available day and night for the receipt of notifications. All the data were checked against information received from other sources and by direct contact with the hospital where the casualty was located. The decision as to the need and appropriate time of transfer of a casualty to an R.A.F. hospital depended upon the type of injury, the fitness for transfer, and the location of the casualty. In cases of doubt the patients were visited by an R.A.F. consultant or specialist. Eventually, nearly all air-crews were transferred and orthopædic cases, burns, head injuries, and chest injuries were speedily segregated into specialized centres. The transfer was made by road, rail, or air, according to circumstances; as time went on more and more use was made of air ambulances in suitable cases.

Provision of First Aid.—In single-seater aircraft first-aid outfits were provided in small bulk carried by the pilot, generally on the parachute harness; in multi-seater aircraft more elaborate outfits were installed in positions accessible to different members of the air-crews. These outfits contained only such necessities as could be used by the air-crew themselves; this, however, included anti-burn jelly, morphia, and a tourniquet in the use of which the air-crews were instructed by the Squadron Medical Officers.

Station Sick Quarters.—On operational stations, the provision of surgical aid was installed in the decontamination centres. These blast-proof and gas-proof buildings, together with the adjoining 'Sick Quarters' with which they communicated, were miniature hospitals.

Tiers of bunks were installed and the adjoining walls piped for oxygen, so that each bunk had its own oxygen delivery point flow-meter and mask. Oxygen was delivered from a battery of cylinders, and spare cylinders, generally of the aircraft type, provided. Each bunk was fitted with an electrically heated blanket or a heat cradle, a switch panel of the wall allowing the individual control of each cradle. Supplies of blood, plasma or serum, sterile distilled water, the necessary transfusion apparatus, were at hand, always ready for use. Surgical equipment necessary for emergency treatment—arrest of hæmorrhage, tracheotomy, drainage of cavities—splints, plaster, and dressings, completed the equipment. In addition, a few stretchers were fitted with their own oxygen apparatus (cylinder, pressure gauges, economizer, and mask), and in some ambulances provision was made for transfusion of blood. The Station Medical Officers were thus provided with all necessities for resuscitation and first aid, and good use was made of these facilities not only for the casualties returning from operational sorties, but also in case of enemy attack on the station.

In addition, mobile surgical teams for general surgical aid, and for orthopædic and maxillo-facial cases, were located at a few selected stations. These teams were primarily intended to proceed to the scene of the accident, but use was made of them on occasions to assist small hospitals after air raids.

SPECIAL CENTRES

The frequent occurrence of a certain type of injury in air-crews led to the development of special centres. For these, special equipment was provided, selected medical officers appointed, and orderlies trained. A high degree of specialization was achieved, with consequent diminution in morbidity, a more rapid functional recovery, and an earlier return to flying duties.

Burn Centres.—Five burn centres were established in R.A.F. hospitals and one in a civilian hospital under the personal direction of Mr. A. H. McIndoe, the civilian Consultant in Plastic Surgery. The complex problem of the treatment of burns required the use of special laboratory facilities, burn wards, constant-temperature saline baths, operating theatres reserved for plastic surgery, and facilities for recreation of patients requiring prolonged hospitalization. The young medical officers in clinical charge of these departments were chosen for their special skill, knowledge, and interest in burns and plastic repair. No facility was denied to them, and the guidance, advice, and example of Mr. A. H. McIndoe was constantly at the disposal both of the air-crews and the medical officers. It is claimed that from first to last, however long and complicated the treatment, air-crew victims of burns will find within their own hospitals all that surgery can achieve.

Maxillo-facial Units.—These units are generally associated with the burn centres and plastic surgery departments. In addition to medical officers, dental officers have been specially trained, and dental laboratories and workshops provided, and cases are transferred to such units at the very earliest moment.

Fracture Departments.—The segregation of all fractures into fracture wards under trained orthopædic surgeons, the transfer of air-crews to these centres, and the creation of an elaborate and highly efficient orthopædic organization is primarily the result of the relentless labours of Mr. Watson-Jones. This organization, with its wards, plaster-rooms, X-ray facilities, detailed record keeping, deals with a vast number of cases. Its achievements consist not only in the actual treatment of fractures with the concomitant improvement in results and shortening of the period of incapacity, but equally in the pure surgical advances. Although fractures in the R.A.F. air-crews do not differ from those met in other Services in war-time, some fractures are commonly the result of flying accidents, and certain injuries are more frequent than in other Services. Multiple fractures are common; three or even four distinct injuries may be found in the same patient. Fractures of the talus with associated injuries of the ankle-joint, fractures of the spine, injuries of great severity with vast comminution of fragments are met with frequently. The severity and multiplicity of injuries has of necessity led to a greater conservatism in treatment than would have been the case if solitary injuries only had had to be dealt with. That this segregation of cases, unified control, and constant supervision has been justified is illustrated in a report by Wing Commander W. D. Coltart on a series of over 600 cases of fracture of the tibia and fibula and of the femur. A critical analysis of the cases leads him to conclude that " These fractures both of the tibia and of the femur which have been treated throughout in R.A.F. orthopædic units have on the whole united more quickly than those transferred from other centres, especially if transferred more than fourteen days after injury. The early transfer of these fractures should therefore be insisted upon." In fractures of the talus with associated injuries of the ankle, the immediate treatment is even of greater importance, and such injuries must be considered as first emergencies if functional recovery with minimum disability is aimed at.

Rehabilitation Centres.—Special centres for rehabilitation for air-crews have been established. Besides physical rehabilitation, facilities are provided for technical rehabilitation. These centres are equipped with gymnasiums, playing fields, swimming pools, and tennis and squash courts. Physical training instructors and medical officers receive the patients on their discharge from hospital, nearly always still encased in plaster. They are taught to walk, to run, to dance, to use their muscles, to discard crutches, sticks, plaster casts, and the self-consciousness of their disability. Systematic and graduated exercises lead to physical recovery. During the period of recovery

technical rehabilitation is commenced as soon as the physical condition permits. Pilots fly in a Link Trainer, navigators, bomb-aimers, wireless operators, air gunners, flight engineers are provided with the elaborate and intricate instruments of their speciality. The value of the technical re-education at this stage is both physical and psychological. The air-crew become aware that they are again air-crews and no longer patients or cripples.

Assessment of Fitness for Flying.—All air-crews, injured or otherwise incapacitated, pass through a Board before returning to flying duties. The degree of disability is estimated in its relationship to their flying duties. Cases of frost-bite, burns, or other vascular disturbances are reviewed with the possible effects of altitude or cold on their previous injuries. If the physical disability leaves a doubt as to their safety or efficacy in the air—a report is obtained from the executive as regards the particular point in doubt.

SUMMARY

The scheme of surgical treatment from the time of injury in the aircraft to the final disposal and return to duty has been indicated. Facilities provided by the Royal Air Force in special surgical departments exceed even those of teaching hospitals in peace-time. These facilities and the selection of specialized staff have contributed to the advances made in the treatment of injuries of all kinds. The guiding principle is to provide air-crews with the best possible treatment, particularly in the case of injuries resulting from flying and enemy action. The final aim and object is to obtain the maximum operational efficiency in the shortest possible time.

I record with grateful acknowledgement my indebtedness to Air-Marshal Sir Harold Whittingham for many facilities without which this paper could not have been written and for permission to publish it. My thanks are also due to Dr. Bradford Hill for revising the statistical data of the section on head injuries ; to Wing Commander G. Morley, Squadron Leader D. N. Matthews, and Flight Lieutenant Bodenham for the clinical notes of some of the case records, and for some of the illustrations.

THE TREATMENT OF BURNS AND WOUNDS WITH SKIN LOSS BY THE ENVELOPE METHOD*

By R. P. OSBORNE

In July, 1941, there were published in the *British Medical Journal* four articles on " The Treatment of Burns and Wounds by the Envelope Method " (Bunyan, J. ; Hudson, R. V. ; Pearson, R. S. B., et al. ; and Hannay, J. W.). Since then little has appeared in the literature on the subject : the object of this paper is to set forth some personal observations following upon the employment of this method on cases admitted to the Plastic Surgery and Jaw Injury Service of the Stoke Mandeville Hospital.

Envelopes have been used on 31 cases in nine months. The cases fall into three groups :—

1. New burns—i.e., within 48 hours of the injury	6
2. Old burns	12
3. Unhealed wounds with skin loss of varying degree	13

The numbers are too small to tabulate results, but several illustrated cases will be described.

OBJECTS OF TREATMENT

The objects of treatment are : (1) To prevent infection and cross-infection ; (2) To obtain a skin covering as soon as possible ; (3) To eliminate pain ; (4) To prevent deformity ; (5) To maintain free function ; (6) To reduce to a minimum the length of time between receipt of injury and return to normal duty.

Our experience shows that the envelope method fulfils these objects in a praiseworthy manner.

1. Whenever hæmolytic streptococci were present in the lesion at the time of applying the envelope, these disappeared. In some cases the aid of sulphanilamide insufflations was required.

In one instance (*Case* 6) when the envelope was removed before healing was complete, hæmolytic streptococci reappeared. There was not a single case of hæmolytic streptococci appearing in an envelope when it was known to be absent at the time of application.

2. In cases without full-thickness skin loss, healing was obtained in the envelope except in one or two instances, when small areas remained unhealed. Where there was full-thickness skin loss epithelialization has been greatly assisted : small areas of third-degree burns have healed completely. Large areas of skin loss have been rendered suitable for skin-grafting immediately, after which the envelope method has been continued.

3. The relief of pain has been dramatic. Young patients have been admitted terrified at the thought of having their dressings changed : envelopes have been applied and within one or two days at the most these patients have been free from pain and confidence has been re-established ; their outlook has changed and the general condition has already begun to improve.

4. There has not been in this series a single instance of deformity arising during treatment in an envelope.

* From the Plastic Surgery and Jaw Injury Service, Stoke Mandeville Hospital, Aylesbury.

5. In limb lesions 100 per cent function was regained in all cases except one (*Case* 10), where there was long-standing ankylosis of the ankle prior to the application of the envelope.

6. Rehabilitation treatment was given to all the cases and at the time of discharge they were fit to resume their normal duties. The time spent in hospital compares most favourably with other methods of treatment.

TECHNIQUE

Sterilization of the Envelopes.—The new tie-on type of Bunyan-Stannard envelope has been used throughout (except for the smock in *Case* 2). It was decided to make efforts to sterilize the envelopes, because: (*a*) When taking smears from the inside of the envelopes as supplied and before use, the *Staph. albus* had been found on more than one occasion. Since these organisms can be found, it is reasonable to assume that the streptococcus also might survive in the envelope. (*b*) Having taken every precaution to render the wound as clean as possible, it is just as fitting to apply a sterile covering as to apply a sterile dressing in other methods.

Simple soaking of the envelope in strong solutions of Milton prior to application of the bag does not always get rid of the *Staph. albus*, and it was therefore decided to attempt dry sterilization. The means employed was 10 lb. steam pressure for ten minutes in the hospital autoclave ordinarily used for the sterilization of rubber gloves.

The envelopes were considered to be too tightly folded and in too numerous folds as supplied in their cellophane covers. These latter were therefore discarded and the envelopes fully opened out and then folded three times. One of these was then placed, together with a test packet containing strains of *B. subtilis* (as used by the L.C.C.) in a linen bag similar to those used in most E.M.S. hospitals for the sterilization of gloves and dressings. After ten minutes in the autoclave it was found that the *B. subtilis* had been killed. The next stage was to fold a dozen envelopes in the same manner and place these in a canvas bag. Test packets of *B. subtilis* were used: (*a*) Two at each end of envelopes 1, 6, and 12; (*b*) One between envelopes 6 and 7; (*c*) One under the flap of the canvas bag.

This test showed that the *B. subtilis* was not killed. It was repeated in exactly the same way except that wherever a test packet of *B. subtilis* was placed another containing *Staph. aureus* was used. The result of this was that the *Staph. aureus* was killed in every packet, but once more the *B. subtilis* escaped.

We were advised by a pathological colleague that the killing of the *Staph. aureus* could be safely taken as indicative of satisfactory sterilization.

Effect of Sterilization upon the Envelope.—Observations were made as follows:—

a. The material became slightly yellower, but this did not interfere with its clarity.

b. Repeated sterilization produced a deeper yellow colour and the clarity was slightly reduced each time.

c. The seams remained intact.

d. The texture remained unaltered.

e. Seamed edges tended to adhere to each other, calling for delicate handling when applying the envelope if tears were to be avoided. To overcome this, grease-proof paper was inserted between the folds and this measure was a success. Particular care is necessary to avoid adhesion of the tying-on slips to seams, for the former are readily torn.

f. The inner surfaces tended to adhere in a patchy manner, but this is avoided by inserting a layer of grease-proof paper into the envelope.

g. The inner surfaces of the inlets and outlets became adherent and this proved to be a tiresome complication, because of the time which had to be spent in a careful separation of the edges with forceps before the glass tubing used for irrigations could be inserted. To overcome this the adhesive seals already applied by the manufacturers were removed and the inner surfaces of inlets and outlets well powdered before sterilization. In removing the adhesive seal, some of the adhesive material was left on the outer surface of the inlets and outlets; in order to prevent these areas adhering to other parts of the envelope in folding, they were cleansed with ether.

Storage of Sterilized Envelopes.—With the knowledge that at any time with short notice several cases of burns might be admitted, it was considered that a store of already sterilized envelopes should be available immediately on demand. To keep them in the canvas bag was not considered wise, for quite apart from putting a number of bags out of circulation for an indefinite period, they are not sufficiently air-tight and are not easily stored. To overcome these objections a layer of grease-proof paper was placed inside the envelope (*f, above*) and one on each side, so that when the envelope was folded into three, no two surfaces of the envelope came into direct apposition with each other. The envelope was then loosely tied with cotton to keep the paper in place and the type of packet written on the paper.

After sterilization the envelopes were inserted into previously sterilized paper envelopes large enough to make insertion an easy procedure. The paper envelope was now sealed and the type of envelope it contained recorded on the outside. The insertion was carried out by a member of the theatre staff who had 'scrubbed up' and donned the usual cap, mask, gown, and gloves.

By this means a considerable number of envelopes can be stored in a small space, amply justifying the time and trouble involved, which is always much less than the description suggests.

Steps in the Technique of Application of the Envelopes.—The general treatment follows the usual lines and will not be discussed here. An anæsthetic is usually given for the application of

the first envelope : gas and oxygen or some other form of light anæsthesia is sufficient.

1. Arrange mackintosh sheeting as a gutter underneath the area to be treated so that the fluid can readily flow into a receptacle.

2. Remove dressings previously applied.

3. Photograph.

4. Take smear from wound and send for bacteriological examination.

5. Under a continuous stream of 1 per cent electrolytic sodium hypochlorite in tap water 1–5 at 110° F., cleanse the wound, using gauze swabs : remove all loose sloughs and totally destroyed soft tissue with the aid of scalpel, scissors, and dissecting forceps. The area should be oozing blood at the end of this stage, which occupies ten to fifteen minutes and requires five to eight pints for a limb.

6. Apply a sterilized envelope sufficiently large to allow free movement of the limb.

7. Continue to use the same solution, irrigating through the inlet by means of a piece of glass tubing 7–8 in. long angled at 45° in its distal 2 in. attached to the rubber tubing leading from a large container, using five pints for a limb. The solution is allowed to escape from the outlet as fast as it runs in so as to get the maximum chemical and mechanical effect.

8. Allow the envelope to drain for 5–10 minutes.

9. Dry the interior of the envelope by means of air blown through a sterile cotton-wool filter, using an electric hair-drier or an electric suction machine applied in the reverse manner. This process takes 10–15 minutes, for it must be thorough.

10. Apply adhesive seals to the outlets and inlets.

Subsequent Irrigations.—These are carried out, without anæsthesia, three or four times a day in the ward or in a side room set apart for the purpose. A concentration of 1 per cent electrolytic sodium hypochlorite in tap water 1–20 is used, five pints to a limb, 100° F., from a large container through sterile rubber and glass tubing : the fluid runs out through the rubber tubing attached to an outlet into a receptacle, the limb being placed so that the outflow is as free as possible. The envelope is drained and dried as before and every few days a smear for culture is taken of the wound surface prior to commencing an irrigation. As healing progresses and discharge between the irrigations diminishes, the number of irrigations can be reduced to two a day and the concentration of the solution to 1–100.

Important Points in After-care.—

1. *Pain.*—The irrigation is usually painless, but a few patients do complain of a smarting sensation which may be severe and this can be overcome by reducing the concentration as low as 1–100 and after a few irrigations increasing by stages until the 1–20 is reached again, when it will be found that this is now tolerated.

2. *Tingling.*—This occasionally occurs, but is not unduly distressing and disappears when the irrigation has ceased.

3. *Temperature of the Irrigation Fluid.*—This should be as constant as possible (100° F.), for in the early stages of treatment patients are apt to be very sensitive to variations in temperature.

4. *Dermatitis : Furunculosis.*—These may be noticed in the area of undamaged skin enclosed in the envelope after two or three weeks' treatment for reasons not understood, but possibly due to inefficient drying. These complications need not interfere with the treatment and soon clear up when the envelope is removed.

5. *Control of Infection.*—The smear taken just before the application of the envelope indicates the organisms present in the wound. Organisms usually found on the skin will continue to be found throughout treatment. Others such as hæmolytic streptococci and *Staph. aureus* will disappear. In a few cases the aid of sulphanilamide powder insufflated through an inlet on to the wound after the drying process is over has to be employed. Occasionally the *Staph. aureus* still persists, but its presence has not delayed healing. Bacteriological examinations can be made at will by taking smears through an inlet immediately prior to an irrigation.

6. *Exuberant Granulations.*—These can be very easily controlled by a pressure dressing of wool and crêpe bandage applied outside the envelope between the irrigations.

7. *Œdema and Splints.*—When there is œdema of the hand and fingers at the time of application of the envelope it is important that this be reduced as quickly as possible, for otherwise function may be permanently impaired. Splints, either in the form of plaster or metal cock-up, are applied outside the envelope : the limb is then elevated with flexion of the elbow by placing it in a sling and suspending it by a pulley and weight from a Balkan beam. The splint is removed for irrigation purposes and whilst this is proceeding active movements are encouraged.

8. *Restoration of Function.*—The size of the envelopes allows of active movements which are encouraged from the beginning, preferably under the guidance of a physiotherapist. A hand in an envelope is soon regularly used at meal times and for writing.

9. *Delayed Healing.*—Healing usually progresses steadily in the envelope, but in a few patients the final stages may be delayed. This is sometimes overcome by reducing the concentration to 1–100 : in other cases final healing has occurred only after removal of the envelope and a change to sulphanilamide, tulle gras, and saline gauze dressings.

10. *Opacity of the Envelope.*—Where there is much exudation between irrigations the clarity of the envelope soon diminishes. The addition of ammonium lauryl sulphate (60 min. to 5 pints) to the irrigating solution helps to preserve the clarity.

11. *Life of the Envelope.*—As judged by the appearance of minute holes, especially near the seam, the life is between three and five weeks. The more active the patient, the shorter the life

of the envelope. An anæsthetic is not required for the renewal of the envelope unless it is desired to assist the separation of adherent sloughs by a further irrigation with the more concentrated solution.

12. *Condition of Skin upon Removal of the Envelope.*—In some cases, especially deep second-degree burns, the regenerated epithelium is rather fragile, tending to form blebs if subjected to friction, e.g., when using a billiard cue. These cases, together with all those where skin has been grafted, improve with a course of massage with lanolin (in the more extensive lesions preceeded by wax baths) for 10–14 days, a measure which can, with advantage, be continued at home by the patient himself.

Skin-grafting during Treatment in an Envelope.—Save in the smaller areas, where there is full-thickness skin loss, time is saved and healing rendered more stable by applying Thiersch grafts. This can only be carried out with any certainty when the hæmolytic streptococcus has been eliminated, as determined by three successive negative reports on smears taken from within the envelope. Exuberant granulations can be flattened by applying a pressure dressing outside the envelope, as already mentioned, between irrigations for the 48 hours immediately preceding the grafting. The amount of discharge between irrigations is a useful guide to the most suitable type of graft. If this is minimal, sheets of graft can be applied with good chance of complete 'take'. Free discharge from granulations, on the other hand, lifts off such sheets and small grafts of the 'pinch' or 'chess-board' variety, which would allow free escape of discharge, have proved more suitable.

Grafting Technique Employed.—

1. The donor area on leg, arm, or abdominal wall is prepared in the usual manner.

2. Under an anæsthetic this area is carefully towelled off, the graft cut, and a dressing applied immediately to the raw surface.

3. The envelope is now removed and the unhealed area towelled off and washed in normal saline.

4. Either: (*a*) Sheet grafts are applied, anchored with marginal sutures, and covered with a layer of tulle gras; or (*b*) Chess-board grafts are cut in the manner described by Gabarro (1943).

The sheet of graft is spread out, raw surface upwards, on a layer of the paper found between the pieces of tulle gras in the tins supplied by the manufacturers. It is then cut into strips ¾ in. broad with quick cutting movements of sharp scissors. These strips with their adherent paper are then laid upon another piece of the same type of paper in rows ¾ in. apart: this second piece of paper is cut into strips ¾ in. wide in the opposite direction, so that the resulting pieces of graft are now ¾ in. square. These strips are then applied to sheets of tulle gras so that the squares of graft form a regular chess-board pattern and in this form they are applied to the wound.

5. An envelope is immediately applied and outside this on the grafted area a pressure dressing of wet gauze, wool, and crêpe bandage.

6. *After-treatment.*—The pressure dressing is removed on the third day: the envelope is gently lifted off the tulle gras, and an irrigation (1–20) carried out, taking care to avoid directing the stream on to the grafts. Thereafter irrigations are carried out twice daily and the external dressings dispensed with on the seventh day. The pieces of paper and tulle gras are washed away in a few days by the irrigations, and are removed through an outlet.

ILLUSTRATIVE CASES

RECENT BURNS

Five cases, all of second degree, have been treated by the immediate application of envelopes:

Case	Areas Burnt	First-aid Treatment	Age of Burn	Days in Envelope	Days in Hospital
A	R. lower leg under elastic stocking covering healed varicose ulcer	Salad oil	3 hr.	27	30
B	Dorsum both hands, wrists, and finger	Tannic acid jelly. Saline compresses	4 hr.	left, 10 right, 36	40
C	Face. Anterior and posterior aspect hands	Saline compresses	4 hr.	13	34
D	Face. Dorsum left hand	Nil	4 hr.	9	18
E	Dorsum both feet	Saline compresses	6 hr.	9	12

in all *Staph. aureus* was grown from smears taken at the initial cleansing. All healed soundly without cross-infection (a large furuncle appeared on the right wrist of *Case C* from which *Staph. aureus* was grown, and this delayed final healing). Full movements were maintained throughout, all the hand cases using knives and forks at their meals.

OLD BURNS

(*i.e.* 48 *hours or more*)

Eleven cases have been treated, the time between receipt of injury and admission to this hospital varying from three days to two years. Of these 3 were naval ratings (*Cases* 1, 2, and 3) admitted 72 hours after partaking in the raid on Dieppe. They were all members of the same gun crew and were burnt when an enemy shell exploded close to them. Within half an hour gentian violet solution had been applied, with one further application on reaching land, and cotton bandages applied. It is interesting to observe that *Case* 3 stated he felt his fingers slowly "contracting", owing, he thought, to the drying of the solution.

Case 1 (183).—Admitted on Aug. 23, 1942, with second-degree burns of whole of foot, ankle, and heel, areas of third-degree burns on dorsum, all infected.

TREATMENT.—Application of envelope and irrigations; these caused pain and the strength had to be reduced to 1–100, but at the end of the week a 1–20 solution was tolerated without pain. Active movements were encouraged from the beginning; 80° flexion of ankle was possible on the 16th day. Envelope removed after 26 days with healing completed except in two areas which rapidly responded to 5 per cent sulphanilamide ointment. The new epithelium was purplish in colour, tending to break down in one or two areas when wearing shoes. Kept off weight-bearing until the 58th day, using crutches in the meantime and being given massage and wax baths.

Discharged Nov. 12 (81st day) with 100 per cent function and sound epithelial covering.

BACTERIOLOGY.—Hæmolytic streptococcus on the application of envelope.

Case 2 (177).—Admitted Aug. 23, 1942, with second-degree burns involving almost the whole of the face, both arms from shoulders to fingers, including the axilla and scapula area on the left side. Several scattered areas of third-degree burns on the arms. Multiple blisters and large areas of raised coagulum.

TREATMENT.—Taken to the theatre on day of admission and all areas cleansed with normal saline, dried sulphanilamide powder applied and 1 per cent gentian violet solution applied to the upper arms, tulle gras and saline compresses to the face and hands. For the next three days saline baths for the hands twice a day: encouraged by the physiotherapist to move all joints. He was extremely uncomfortable, perspired freely, and it was a matter of great difficulty to keep the arms dry. Mr. Kilner then saw him and advised the application of an envelope in the form of a smock. This was applied on the third day and there followed a dramatic improvement in his general condition and outlook. He was comfortable, tolerating four-hourly irrigations very well and co-operating with a full range of active movement (supervised twice a day by a physiotherapist). Between irrigations his limbs were elevated in slings suspended from Balkan beams.

The smock was changed once: he was using both hands at meal times on the 16th day, i.e., 13 days after the application of the smock. On the 26th day the smock was removed except for the left sleeve, as the right side had healed except for one or two tiny areas: the left side was healed in 62 days, save again for similar small areas. Healing was complete throughout on the 69th day, but as in *Case* 1, the new epithelium was purplish and shiny, and blebs formed from time to time. Massage with lanolin was given on removal of the smock, which soon improved the condition of the epithelium.

Discharged 93 days after admission with 100 per cent function of all joints and sound healing. A letter was received from this Naval rating six months later expressing gratitude and stating that his limbs were in sound condition.

BACTERIOLOGY.—Smears taken on application of the envelope and at subsequent dates showed *Ps. pyocyaneus*, *Staph. aureus* and *albus*, diphtheroid bacilli, *B. proteus vulgaris*, and *Str. fæcalis*, but at no time was a hæmolytic streptococcus discovered.

Case 3 (182).—Admitted Aug. 23, 1942, with second-degree burns involving whole of both wrists, hands, and fingers; several small areas of third-degree burns. Second-degree burns of whole of face. Most of the coagulum was raised with pus beneath.

TREATMENT.—Cleansed in the theatre, dried, sulphanilamide powder, tulle gras, and saline compresses applied. Thereafter he had arm baths in normal saline twice a day, the dressings being allowed to float off and fresh ones re-applied after the bathing. He was in poor condition and loathed his baths, as they left him 'exhausted': he was disinclined to co-operate with active movements. On the 5th day he was given an anæsthetic and envelopes were applied to both forearms and hands. Outside these, cock-up splints were applied and the limbs elevated in slings suspended from Balkan beams with the elbows in 90° flexion. Irrigations were carried out four-hourly, the splints being removed, and active movements were encouraged by the physiotherapist. Eleven days after the application of the envelopes he was using both hands at meal times, so that elevation and splinting were discarded altogether during the day time. Six days later healing was complete except for small areas over the knuckles, which reacted well to sulphanilamide ointment. Massage with lanolin followed, but again the epithelium showed a tendency to bleb formation after friction, such as using a billiard cue or a broom. Such exercise was suspended for a few days until his epithelium appeared in better condition.

Discharged 53 days after admission with 100 per cent function and sound epithelium.

Comment.—These 3 cases were the first in which envelope therapy was tried; the striking improvement in the general condition of all three and the uninterrupted progress of healing *with maintenance of function* from the beginning, revealed convincing evidence of the value of the early application of this treatment.

Case 4 (301).—Admitted Nov. 2, 1942. A member of the R.A.F. who eight days previously received extensive scalds on the dorsum of the right foot. Various applications had been used, including gentian violet, liquid paraffin, saline, and acriflavine, the foot being covered with bandages after every treatment. On admission the area was infected, with raising of the coagulum and slough formation.

TREATMENT.—An envelope was applied on the day of admission, changed in three weeks, this being renewed after another three weeks with healing complete save for one small area the size of a sixpenny piece. Wax baths and massage with lanolin followed and active movements had been supervised from the beginning.

Discharged 69 days after admission with full function and sound epithelium.

BACTERIOLOGY.—On admission hæmolytic streptococcus, *Staph. aureus*, diphtheroid bacilli.

Nov. 18: No change.
Dec. 10: *Staph. aureus* and *albus*.
Dec. 16: *Staph. aureus* and diphtheroid bacilli.

Comment.—Hæmolytic streptococcus disappeared during treatment in the envelope. Duration of hospitalization would have been considerably reduced had the envelope been applied immediately after the accident.

Case 5 (422).—Admitted March 11, 1942. A member of the W.A.A.F. who scalded her left lower leg just above the ankle on Jan. 1 whilst on leave. Her own doctor applied gentian violet. On returning to her unit she attended the sick bay three times a day

for dressings and various applications were tried. For seven weeks prior to admission to this hospital she had been in bed in the sick bay having sulphanilamide powder and saline compresses applied to the area three times a day. Apparently from time to time new epithelium was seen growing in from the edges, but this soon disappeared. A few days before admission a generalized rash appeared and persisted. On admission there was an irregular granulating area 4 in. in diameter, with an uneven base, quite clean. There was a generalized hard papular rash with several pustules.

TREATMENT.—Envelope applied without an anæsthetic and in seven days the ulcer had been reduced in size to 1 in × ¼ in. Envelope removed on the 16th day, massage with lanolin following.

Discharged on the 42nd day after admission with 100 per cent function.

BACTERIOLOGY.—Debris only. Culture sterile.

Comment.—An example of over-zealous use of sulphanilamide powder as a local application, and of too frequent dressings.

Case 6 (237).—Admitted Oct. 12, 1942. A child aged 6 years, who received third-degree burns of the right lower leg in May, 1942. She was admitted to the local hospital and three or four weeks later she had fever, cyanosis, pallor, hæmaturia, and was mentally deranged. These symptoms were attributed to poisoning by sulphanilamide, which had been given for two weeks in the form of twice-daily applications of 5 per cent sulphanilamide ointment, 36 hours of generous application of pure sulphanilamide powder, and 24 hours of 0·5 g. by mouth four-hourly. This drug was stopped at once and eusol used as a local application. On admission her general condition was poor, she was frightened at the thought of having the dressings changed, and presented a granulating area involving the whole circumference of the middle-third of her right lower leg. Hæmolytic streptococci were found in her throat and also in the granulating area, together with *Staph. aureus* and *albus*.

TREATMENT.—An envelope was applied and immediately her fear of dressings disappeared, for the irrigations were painless. Her general condition improved, appetite was regained, and she co-operated well with her active movements. The envelope was changed in a month, by which time the hæmolytic streptococcus had disappeared, the other organisms persisting. Healing had progressed very well, but after three weeks in the new envelope little further progress was made although the streptococcus had not reappeared. The envelope was removed on the 43rd day and the unhealed area, measuring 1½ in. × ½ in., was dressed with cod-liver oil. Progress was very slow, and on the 59th day there was a breakdown of the surrounding epithelium, increasing the size of the ulcer to 2 in. × 1½ in., and the streptococcus was grown from the area and from the throat. The wound was dressed with a very small amount of sulphanilamide powder, tulle gras, and saline; this was followed by the disappearance of the streptococcus, so that on the 71st day a Thiersch graft was applied. This failed, coinciding with the reappearance of the streptococcus. Pinch grafts were tried three weeks later, but these failed, the streptococcus persisting in the leg and throat. Tonsillectomy was performed on Feb. 1, 1943, and the leg dressed with saturated sodium sulphate. Four months after admission there was an ulcer 1 in. in diameter anteriorly and four smaller ulcers posteriorly from which the streptococcus was grown. Propamidine was applied on alternate days for 10 days, resulting in the healing of the anterior ulcer and three of the posterior ulcers. A scanty growth of streptococci was obtained from the remaining ulcer. A week later this ulcer had increased in size and a second course of propamidine was given, resulting in a reduction in size, but the organism still persisted. On April 19, i.e., six months after admission, there was an increase in the amount of discharge from the posterior ulcer and there was a small ulcer anteriorly. Propamidine dressings were then applied at intervals of two or three days for a month, by which time both ulcers had healed and during which a negative report was received.

Discharged 10 months after admission with full function and completely healed. Follow-up examinations have been made three and again six months after the date of discharge. The leg is of good shape and the area remains soundly healed.

Comment.—A patient hypersensitive to sulphonamides who carried hæmolytic streptococci in her throat despite tonsillectomy. These organisms had disappeared whilst the leg was in the envelope, only to reappear when this was removed. Propamidine in the dosage recommended failed to bring about complete healing or the disappearance of the organism, but a third trial extending well beyond the ten days brought about a cure.

WOUNDS WITH SKIN LOSS

Case 7 (232).—Admitted Oct. 13, 1942. A girl, aged 17, whose dress caught fire on Nov. 21, 1940, as the result of which she received burns of both thighs, both lower legs, the back, right upper arm and elbow, left hand and elbow.

She was admitted to her local hospital the same day and remained there as an in-patient for six months. During this time various forms of local therapy were tried, including (*a*) acriflavine dressings, (*b*) tannic acid, (*c*) liquid paraffin, (*d*) eusol, (*e*) eucalyptus ointment, (*f*) cod-liver oil, (*g*) small Thiersch graft from lower leg to thigh. Throughout her stay in the hospital she lay flat on her back with a pillow under her knees.

At the end of six months her mother took her home against medical advice: her own doctor paid frequent visits, repeatedly applying tannic-acid spray to the large unhealed areas on the thighs and legs. After seventeen months of this treatment at home she was sent as an in-patient to a hospital in London where she was given a transfusion of whole blood and transferred to Stoke Mandeville Hospital fourteen days later. On admission there was marked pallor of skin, she was thin and under-developed for her age, and was extremely apprehensive at the thought of having the dressings changed. Local findings: (1) Whole of the anterior surface and half the circumference of the right thigh and the upper two-thirds of the anterior aspect and half the circumference of the left thigh were covered with pink protuberant granulations; extreme wasting of the thigh muscles. (2) 45° flexion contracture of both hips and 90° flexion contracture of both knees. (3) Granulating areas about 2½ in. in diameter on the buttocks and middle of the posterior aspect of the lower legs. Pathological findings: Hæmoglobin 65 per cent; colour index 0·7; Group AB. A growth of *Staph. aureus* and diphtheroid bacilli from all areas.

TREATMENT.—Full-leg Stannard envelopes applied under anæsthesia the day after admission, preceded by cleansing of the areas in the routine manner.

Active movements of the hips and knees were encouraged, under the supervision of the physiotherapist, from the beginning. Owing to her apprehension the weakest solutions were used for the first four days, by the end of which she had completely regained her confidence, was cheerful, taking an interest in her ward companions, and co-operating with the physiotherapist. Eight days later Thiersch grafts were taken from the anterior abdominal wall and from the anterior chest wall. The Stannard envelopes were removed and the granulating areas on the thighs, now much cleaner and flatter than on admission, were washed with 1–5 Milton. The sheets of graft were applied so as to form a spiral covering anchored with a few marginal sutures and several smaller grafts were used in the postage-stamp manner, and the whole area then covered with tulle gras. New Stannard envelopes were applied and pressure dressings outside these over the grafted areas. The bacteriological findings at this stage were *Staph. aureus*, *Proteus vulgaris*, and diphtheroid bacilli. The first irrigation was carried out four days later and thereafter once daily for a week, after which the pressure dressings were discarded and irrigations carried out twice daily. All the grafts took, and from then onwards healing steadily progressed. Five weeks later the envelopes were removed; two-thirds of the granulating areas were covered with epithelium, and pinch grafts (50), taken from the anterior abdominal wall, were applied to the remaining unhealed areas. The lower legs and buttocks were soundly healed. Four of the pinch grafts failed to take. Eleven weeks after admission she began to walk without the support of the physiotherapist. At the end of the 14th week all the areas were healed and the muscles had developed well, but there remained 20° flexion contracture of the left knee and 30° of the right. Extension by means of spats made of bandage and Unna's paste was applied for three weeks, which resulted in full correction of the left knee and of the right except for 5°. Walking exercises were resumed, together with the rehabilitation measures: the skin of the thighs broke down in one or two small areas at intervals, but six months after admission all areas were soundly healed, all contractures and her lordosis had been corrected, her posture was excellent, and she walked well and was discharged. She was reviewed as an out-patient six months later. All the areas had remained healed—she had gained weight—could walk two miles with ease and without any sign of œdema of the ankles.

Comment.—Two and a half years elapsed between the date of the accident and full recovery. With treatment in Stannard envelopes and early grafting the greater part of this time would have been avoided. An example of grafting with immediate continuation of envelope therapy.

Case 8 (412).—Admitted March 9, 1943. A child, aged 6, who six days before was in a house bombed during an air raid, receiving third-degree and fourth-degree burns of the posterior aspect of the right elbow and upper two-thirds of the forearm, with 2 in. of the upper end of the shaft of the ulna exposed; third-degree burns of the upper half of anterior aspect of the right thigh and small scattered areas of third-degree burns of the perineum, groin, right ear, and left index finger. He had been given a transfusion of plasma and the burns cleansed, followed by the application of saline compresses. On the third day an envelope had been applied to the forearm, but was removed the next day.

On admission he was in poor general condition, pale, tired, fretful, and apprehensive lest his dressings were to be changed. All the burnt areas were covered with thick slough.

TREATMENT.—An envelope was applied after removal of the slough under a stream of hypochlorite solution. Irrigations of the 1–20 solution were painful, so that the strength was reduced to 1–100 for six days. His general condition improved at once and he was soon eating well and taking a lively interest in his surroundings and fellow patients. The discharge between irrigations was profuse for the first fortnight: on the 9th day a slough separated from the posterior external aspect of the elbow-joint, revealing a defect in the capsule and synovial membrane. An anterior splint of plaster was made to keep the elbow at 90° flexion between irrigations. At the application of the envelope there was a heavy growth of hæmolytic streptococci and *Proteus vulgaris*, but the former disappeared two weeks later, with the use of insufflations of sulphanilamide. On the 17th day chess-board-type Thiersch grafts were applied to forearm and thigh, with immediate application of envelopes. The first irrigation was carried out three days later and thereafter twice daily, using the 1–20 solution. Four of the grafts were much too thinly cut and failed to take, otherwise healing steadily progressed. Seven weeks after admission the arm had healed completely except for the projecting upper end of the ulnar shaft—there was no sign of a communication with the joint cavity and there was a full range of movement. In the thigh 80 per cent of the area had healed and the envelope was changed. In the 9th week this was removed, leaving an area the size of sixpence unhealed. A week later the projecting portion of ulnar shaft was removed as a sequestrum, and was followed by the application of another envelope.

Comment.—An example of the disappearance of the hæmolytic streptococcus during envelope therapy, grafting, and continuing in the envelope, followed by rapid healing. At the time of writing the case is still under treatment: the child has 100 per cent function in all joints, running about the ward, and will be discharged as soon as the upper end of the ulna is covered with sound skin.

Case 9 (145).—Admitted Sept. 4, 1942. A child, aged 10, who two months previously, whilst walking with one foot in the gutter and the other on the pavement, was hit from behind by a motor lorry. He was admitted to the local hospital with a large area of skin loss of the left lower leg. A long leg plaster was applied and removed ten days later, after which he had dressings every other day.

On admission there was an unhealthy granulating area from just below the knee-joint to the malleolus, involving the whole circumference of the leg. There were scattered granulating areas around the right knee and lower leg.

TREATMENT.—Envelopes were applied to both legs, from which were grown *Ps. pyocyaneus*, *Staph. aureus*, and diphtheroid bacilli. On the 19th day the envelopes were changed, the same organisms being found. There was 20° limitation of full extension during active movements of the left knee, and a padded splint of Kramer wire was applied behind the joint in full extension outside the envelope. On the 35th day a sheet of Thiersch graft 5 in. × 3 in. was applied to the left lower leg, covering roughly 50 per cent of the unhealed area—a sheet rather than the chess-board

pattern because the amount of discharge between irrigations was small. An envelope was immediately applied, the first irrigation being carried out three days later and subsequently twice a day with the 1–20 solution. There was a 100 per cent take of this graft, and ten days after applying the graft the splint was discarded during the day, when active movements against resistance were encouraged. On the 63rd day a smear revealed *Staph. aureus* and diphtheroid bacilli; the next day a sheet of Thiersch graft was applied to the remaining unhealed area, followed by the immediate application of an envelope. Thereafter treatment was as before, but this time there was a small area of failure of take measuring 1 in. × ½ in. The envelope was removed 18 days after applying the graft, followed by cod-liver oil dressings. Re-education in walking was commenced, a slow process because of troublesome œdema of ankle and foot after weight-bearing.

In the 17th week after admission he was walking without limp or œdema, with a sound covering of skin throughout; but as the ward was in quarantine because of chicken-pox, discharge was delayed for a further six weeks.

Comment.—An example of successful sheet Thiersch-grafting during envelope therapy in the presence of discharge containing *Ps. pyocyaneus* and *Staph. aureus*. The grafting could have been carried out earlier had envelope therapy been instituted at the beginning.

INDOLENT ULCER WOUNDS

Case 10 (383).—Admitted Feb. 2, 1943. A female, aged 31 years, who had injections for varicose veins in her right leg in March, 1938, followed by septicæmia, suppurative arthritis, and eventually ankylosis of the right hip, ankle, and tarsal joints, and a limited range of movement of the knee. An ulcer 1 in. in diameter immediately below and behind the internal malleolus had remained unhealed for four years.

On admission this ulcer was covered with a firm scab which apparently formed from time to time and then separated, leaving the ulcer as before.

TREATMENT.—An envelope was applied and three weeks later healing was complete. The envelope was removed and a Viscopaste bandage applied to the lower leg: the patient was allowed up from this time.

Discharged 5 weeks after admission—ulcer healed, complete return of function possible prior to admission.

PROGRESS.—She was seen six months later when the skin over the ulcer area was still sound and had not given any trouble since the date of her discharge.

Case 11 (374).—Admitted Jan. 15, 1943. A sailor, who on Oct. 8, 1942, caught his left heel between the moving platform of a gun and the deck of the ship, sustaining a lacerated wound from just below the internal malleolus, running downwards and forwards almost to the outer side of the sole. This extended down to the os calcis; there was no fracture and the wound after excision of the edges was sutured, followed by the application of a lower-leg plaster. This plaster was removed three weeks later, but healing was incomplete. He could not walk because of pain, and local dressings were applied. On admission there was an unhealed area below and behind the internal malleolus 1½ in. × ½ in., pear-shaped, a clean granulating base shallow above and deep below.

TREATMENT.—An envelope was applied, the smear revealing *Staph. aureus* only. Healing was complete in six weeks; he had been using crutches throughout, and in the 7th week re-education in walking was begun.

Discharged 11 weeks after admission with 100 per cent function and fit for duty.

Comment.—This case had defied all efforts with local applications and was referred to this Unit with the suggestion that a skin-graft was the only solution.

Case 12 (350).—Admitted Nov. 19, 1942.—A sailor who received a shrapnel wound resulting in a compound fracture of the right fourth metatarsal. The edges of the wound were excised, fragments of shrapnel removed, and a lower-leg plaster applied. On admission there was an unhealed wound 1½ in. × 2 in. over the dorsum of the fourth metatarsal.

TREATMENT.—An envelope was applied: the smear revealed hæmolytic streptococci. Healing was complete in the 9th week. Thereafter he was given saline soaks, wax baths, and massage with lanolin, followed by re-education in walking.

Discharged 11 weeks after admission with 100 per cent function and fit for duty.

Comment.—Delayed healing due no doubt to unrecognized presence of hæmolytic streptococcus. He was transferred to this Unit with the suggestion that he was a suitable case for the application of a direct flap from the other leg.

CONCLUSIONS

Envelope therapy provides a reliable yet simple method of treating burns and wounds with full-thickness skin loss.

In the majority of our cases we were asked to undertake treatment some time after the original injury: our experience leads us to believe that if this therapy had been instituted at once much time and pain would have been saved, and damage caused by infection prevented. It would appear to be an ideal method of eliminating the hæmolytic streptococcus, and reducing risk of cross-infection to a minimum.

Two further striking features have been the dramatic improvement of general condition and the maintenance of full function in every case.

The method compares favourably with others in common use: the pain and repeated disturbance of newly-regenerated epithelium with constant risk of infection and cross-infection, the bugbear of other methods, are entirely avoided.

SUMMARY

1. The objects of treatment of burns and wounds with skin loss of varying degree are outlined, and it is shown how envelope therapy fulfils these.

2. The technique of sterilizing Stannard envelopes is described.

3. The method of using the envelopes is described in detail.

4. Methods of combining skin-grafting with envelope therapy are explained.

5. Several case histories are given, showing the value of the method in recent and old burns and wounds with skin loss.

I am deeply indebted to Professor T. Pomfret Kilner for constant encouragement and advice whilst investigating this method and in the preparation of the paper; to Mr. Stannard for providing a generous quantity of the new tie-on envelopes; to my colleagues and members of the nursing staff at Stoke Mandeville Hospital for their co-operation and enthusiasm; and, finally, to Dr. F. Hall, Medical Officer of Health for Lancashire, for making it possible for me to be seconded to this hospital for training.

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THE DIAGNOSIS OF THE DEPTH OF SKIN DESTRUCTION IN BURNS AND ITS BEARING ON TREATMENT*

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DURING the air raids of 1940–41, when a number of cases of burns were admitted to the Middlesex Hospital, we were impressed by the difficulty which even experienced observers found in assessing accurately the depth of skin destruction during the acute phase. The prognosis of burns depends very largely on the depth of skin destruction; the principles of treatment of a superficial burn may be quite different from those of a deeper burn, and it is unfair to compare the results of different types of treatment unless it can be proved that the cases were strictly comparable. We therefore decided to see whether histological methods were a practical means of obtaining more accurate information about the depth of skin destruction in burns. Our first investigations were of patients admitted to the hospital with accidental burns, from whom portions of burnt skin were removed and microscoped.

Further to correlate clinical and histological appearances the investigation was extended to burns produced experimentally under standard conditions in the skin of breasts immediately before removal for carcinoma. Our results may therefore conveniently be considered under the two headings: (1) Clinical material; (2) Experimental material.

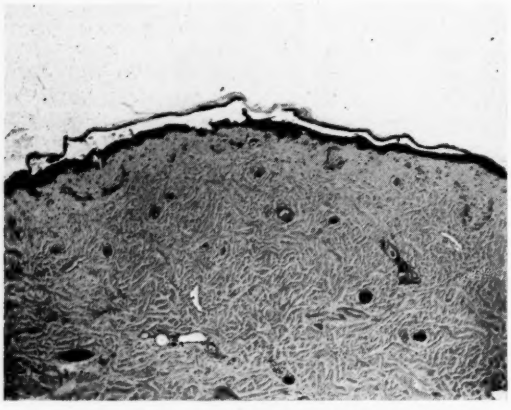

FIG. 18.—Blister with intra-epithelial separation. Hæmatoxylin and eosin. (× 20.)

FIG. 19.—Complete separation of surface epithelium. Hæmatoxylin and eosin. (× 45.)

CLINICAL MATERIAL

HISTOLOGICAL EXAMINATION

The most obvious material for histological investigation in patients with burns is the skin separated by blistering. This shed blistered skin is found to be well fixed by the heat of the burn and makes reasonably good histological material. We find that there are two planes of separation in blistering—through the stratum granulosum (*Fig.* 18) and deep to the stratum malpighii (*Fig.* 19), in the latter all the surface epithelium being lost but leaving hair follicles and glandular structures in the dermis. In neither our clinical nor experimental material have we found anything to support the conception of a plane of

* A preliminary report (unpublished) was read at the meeting of The Association of Surgeons in July, 1943.

separation deep in the epithelium leaving behind the interpapillary epithelial processes (rete pegs) on which so much stress used to be laid in the older classifications. Blistering appears to be an active protective mechanism, and a rapid means for throwing off damaged or killed epithelium. There is no similar rapid vital mechanism for throwing off necrosed dermis, which is separated by the slower mechanism of the formation of a granulation tissue barrier. But at high temperatures, blistering may be simulated by the purely physical process of maceration, in which layers of the dermis may flake off.

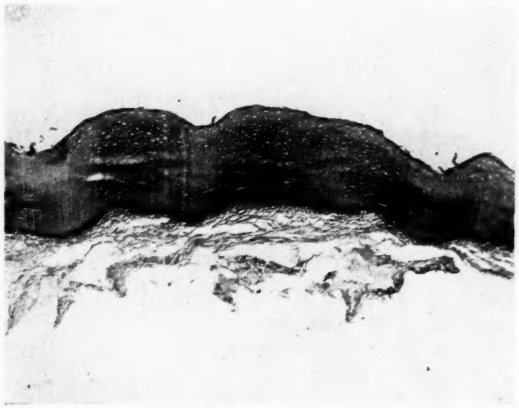

FIG. 20.—From palm of hand. Apparently deep separation, but material consists of keratin and superficial epithelium only. Hæmatoxylin and eosin. (× 45.)

A burn covering a large area constitutes a mosaic work of varying depths of destruction. Clinically, the assessment of the depth of epithelial destruction tends to be influenced by the thickness of the shed blistered skin. But this is misleading, as in situations in which the epithelium is thick, e.g., the palm of the hand, there may be a thick blister even though the plane of separation is through the stratum granulosum, whereas in situations in which the skin is thin, e.g., over the back of the hand or over the breast, a thin and apparently insignificant blister may contain the whole of the surface epithelium. By microscoping representative samples of blistered skin from different areas, a truer picture of the pattern of epithelial destruction may be built up. We have had two striking cases in which a first clinical diagnosis of deep epithelial destruction in the palm of the hand and superficial epithelial destruction in the forearm has been proved by histology to be just the reverse (*Figs.* 20, 21). The subsequent clinical course confirmed the histological findings.

In severe cases of burns it is often easy to recognize with the naked eye that there has been whole-thickness skin destruction from its dead yellowish-white or brown appearance. In many of these cases of obvious whole-thickness skin destruction there is no blistering, the necrosed epithelium remaining fused with the necrosed dermis. But the demonstration that the epithelium shed by blistering is separated at a given plane gives no information as to the state of the dermis deep to the blister and usually the diagnosis that there has been coagulation necrosis of the dermis in addition to the blistering is not made on the immediate appearances but on the progress of the case. It is to this question of the immediate diagnosis of dermal destruction not obvious to the naked eye that we have particularly directed our attention.

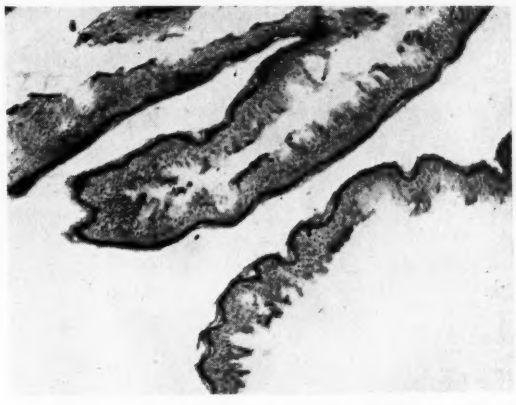

FIG. 21.—From forearm of same case as *Fig.* 20. The apparently thin membrane contains all the surface epithelium. (× 45.)

Coagulation necrosis of the dermis can be recognized histologically. With hæmatoxylin and eosin, it stains slightly more deeply than the normal dermis and presents a condensed and hyaline appearance. We also found that coagulation necrosis of the dermis stains differentially black with Werlhof's elastic stain (*Fig.* 22). Leach, Peters, and Rossiter (1943) have also noted that collagen fibrils damaged by burning show an increased affinity for basic dyes whilst their affinity for acid dyes is decreased.

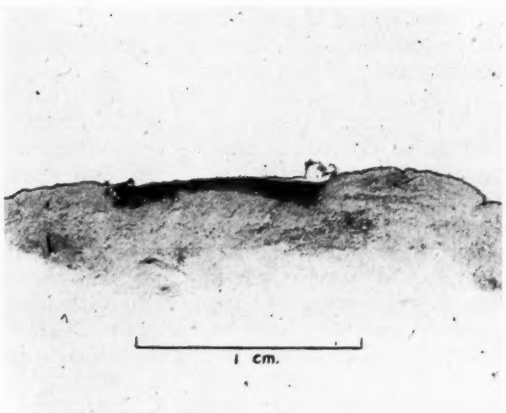

FIG. 22.—Experimental burn stained by Werlhof's method. (× 2·75.)

FACTORS IN HEALING

With surface epithelial destruction only, even if complete, rapid primary epithelialization in

situ should in theory be the rule if the hair follicles and glands in the dermis are not damaged either by the original burn or subsequently. As we have already stated, there is no evidence for regeneration from the interpapillary processes of the skin (rete pegs), and from our observations it seems almost certain that the areas of regeneration formerly attributed to this cause are in reality derived from the ducts of follicles or glands. The importance of these dermal epithelial structures has been emphasized in recent years by a study of the donor area in partial-thickness skin-grafts (e.g., Brown, 1943). *Fig.* 23 illustrates a section of such graft from one of our cases, from which it can be seen that the whole surface epithelium has been removed. Yet re-epithelialization of the donor area was complete in 14 days. Therefore, in burns with surface epithelial destruction only, the object of treatment should be to combat factors tending to destroy, damage, or interfere with the growth of the epithelial structures in the dermis. The chief damaging factors are three: sepsis, œdema, and trauma, either traumatic dressings or the trauma of unrelieved weight-bearing. We have, like others, found evidence to support the importance of these factors, of which sepsis is the chief, and probably the main advances in the modern treatment of burns derive from chemotherapeutic advances in combating sepsis. Chronic œdema is a recognized inhibiting factor in healing and is now as a routine combated by gravity or by pressure dressings. The importance of the trauma of unrelieved weight-bearing is less generally recognized. It is frequently seen in the delay in the healing of the skin over the calf and over the inner side of the elbow, points on which the weight of the limb in bed particularly bears. It is a special problem in burns involving the whole circumference of the trunk.

FIG. 23.—Section of skin-graft. Shows the line of removal in dermis passing through glands and hair follicles. (× 45.)

Cases with dermal destruction present a different problem. The English school of plastic surgery (e.g., McIndoe, 1940) deserve the main credit for emphasizing that in these cases the object of treatment should be to replace the skin destroyed by grafted skin as soon as possible. In many cases, the diagnosis of complete skin destruction is easy clinically, and a primary débridement and skin-grafting is possible. In the majority of cases, however, a diagnosis of the degree of dermal destruction is not possible in the acute stage, so that the standard treatment is expectant, with secondary grafting during the granulating phase. If sample pieces of dermis are cut out and examined microscopically, the degree of dermal necrosis can be seen. But this method has obvious disadvantages in practical application.

APPLICATION AND LIMITATIONS OF METHOD

On a histological basis, burns of the skin can be classified in two groups: (1) Burns with surface epithelial destruction only; (2) Burns with surface epithelial destruction plus varying degrees of dermal destruction. The first group can again be subdivided into: (*a*) Superficial blistering; (*b*) Deep blistering.

The classification of burns into 1st, 2nd, and 3rd degree and so on, is undesirable owing to the variety of classifications and consequent confusion. For clearness, in describing a burn, the depth of tissue destruction should be stated in words.

In many cases it is obvious that there is coagulation of the dermis, but in most it is impossible to be certain on the point clinically, and it is in these instances that histological control is especially valuable. Great assistance is given if examination of the material shows that the separation is intra-epithelial in character, as in these cases dermal damage is improbable; the material is less valuable if, as is frequently the case, there is complete shedding of the surface epithelium, as there is usually no indication of the presence or amount of underlying dermal damage. Another objection to the method too, is the time that must elapse before the section is produced. It is these limitations that have led us to carry out experimental work to find a rapid method for estimating the degree of dermal involvement.

EXPERIMENTAL MATERIAL

In an endeavour to find a rapid method of assessing the depths of burns, we made some experimental burns on the skin of breasts immediately before removal for carcinoma.

Standardization of Technique.—After the trial of various methods for producing experimental burns, including diathermy and a glass test-tube, we finally used as a standard a metal test-tube approximately 1 cm. in diameter containing paraffin wax into which was inserted a centigrade thermometer which passed through a double perforated cork. The metal of the test-tube transmitted heat better than glass, and the fear of breaking was absent. The test-tube

was heated up to the desired level and its base applied for the determined time. The skin used was that of the breast at the beginning of an operation for carcinoma. The number of applications to any one breast varied, but was usually four or five. Note was made of the temperature and time of each application and a comparison subsequently made with the histological appearances. This procedure gave the opportunity for the study of the appearances of the whole thickness of the skin after burning, and not merely of the shed blistered skin as in most of the clinical material.

Results.—There is no absolute response of skin to a given temperature for a given time. The effects may vary both with the condition of the skin and the burning agent. For example, when, in the earlier stages of the investigation, we used a larger test-tube than we finally used, the burn effects for a given temperature and time were more marked, owing presumably to the greater cooling effects of the blood-vessels the smaller the area burnt. With our standard technique, we found that at 80° C. for 10 seconds there was complete separation of the epithelium without histologically demonstrable dermal changes; above this temperature increasing degrees of dermal necrosis could be seen.

Clinical Use of Stains.—We have already noted that coagulation necrosis of the dermis stains black with Werlhof's elastic stain. This finding led us to explore the possibility of the use of a stain clinically on burnt areas which would pick out the areas of dermal necrosis. The most satisfactory so far has been a modified Van Gieson's stain (picro-fuchsin)—a 0·2 per cent solution of acid fuchsin in a half saturated solution of picric acid in water (approximately 1 per cent). This is normally bright red in colour. If applied to an area without dermal necrosis the area stains red; such an appearance is seen in the donor area of a skin-graft or in a burn with only surface epithelial destruction after the blister has been wiped off. With minor degrees of dermal necrosis a yellowish tinge appears, and where this necrosis is marked a bright yellow tinge results without any red. The necrosed dermis seems to pick out specifically the yellow of the picric acid. We suggest that by some such method of differentiation as this, a large number of cases of dermal necrosis may be recognized clinically in the acute phase, and treated by primary débridement and skin-grafting.

SUMMARY

1. An attempt has been made to achieve by histological methods a greater degree of accuracy in estimating the depth of destruction in skin burns.

2. A standard technique for producing experimental burns in human skin is described.

3. Histological examination of the shed blistered skin is of value in the determination of the depth of damage and in the control of treatment of superficial burns.

4. Such examination is especially valuable if it shows the plane of separation to be intra-epithelial; it is of less value if it shows complete epithelial separation, as there is no indication of the presence or extent of the underlying damage.

5. The degree of dermal destruction can be assessed by differential staining of whole-thickness skin sections, but the taking of such sections on a large scale has practical objections.

6. Attempts have been made to find a stain which, applied to the burnt area in the patient, will give some naked-eye indication of the degree of dermal involvement. A modified Van Gieson's stain has been found useful for this purpose.

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RECENT ADVANCES IN THE TREATMENT OF CARCINOMA OF THE MOUTH AND JAWS

BY T. H. SOMERVELL

NEYYOOR, TRAVANCORE, S. INDIA

IN the coastal districts of South India and Ceylon epithelioma of the mouth, including tongue, jaws, cheek, and lips, is extremely common, and occurs far more frequently than cancer or sarcoma in all other situations put together. Twenty years' experience of treating this variety of carcinoma in a large mission hospital in South India (The London Mission Hospital, Neyyoor, Travancore) has enabled the writer to study, and to practise extensively, various methods of treatment —by operation and by radium and X-ray therapy, and by these latter combined with operation—and to devise certain improvements in technique which, he feels, should be more widely known.

Out of the 10,480 operations for malignant disease (*Table I*) performed in this hospital during the years 1923–42 inclusive, 8439 were done for epithelioma of the mouth, including cheek, lips, tongue, and jaws, these operations being performed on 4853 patients. Of these the number of cases of epithelioma in the various situations is shown in *Table II*.

Table I.—Number of Operations for Malignant Disease in Various Situations Performed at Neyyoor Hospital, during the Years 1923–1942 inclusive

Mouth :	
Upper jaw	349
Lower jaw	1338
Cheek	2177
Tongue	623
Diathermy of Cheek	356
Glands	2590
Breast	113
Penis	171
Rectum	48
Cervix	558
Skin	316
Larynx and pharynx	62
Other	277
Abdominal :	
Stomach	87
Ovary	23
Intestine	14
Total operations for carcinoma :	
Primary	9129
Secondary	996
Sarcoma, etc.	355
Total operations for malignant disease	10,480
Total operations for malignant disease of mouth	7445
Total patients with malignant disease of mouth	4853

Table II.—Site Incidence of Epithelioma of Mouth

Cheek and lips	2533 (52 per cent)
Lower jaw	1338 (28 per cent)
Upper jaw	349 (7 per cent)
Tongue	633 (13 per cent)
Total cases	4853
Separate operations on glands	2590
Plastic operations, tube-flaps, etc.	996
Total operations for carcinoma of mouth, 1923–42	8439

That this large number of cases of buccal carcinoma should have been dealt with in a single hospital of 200 beds in South India is a remarkable fact, and my colleague Dr. I. M. Orr and I studied the subject for some years; Orr (1933) made a survey of some 669 cases, with regard to their habits of betel-nut chewing, their diet, social status, etc., and published the results, including several definite findings which mainly have to deal with the constituents of the betel-nut and its concomitants.

It is not my intention to discuss in this article the question of aetiology, as the findings recorded in the above paper ten years ago still seem to afford a fairly complete and satisfactory explanation of the high incidence of epithelioma of the buccal cavity in certain parts of South India and Ceylon. It may, however, be interesting to summarize them as follows :—

1. Chemical irritation due to the alkaloids produced by the action of lime on the tobacco chewed with the betel leaf and areca nut. The more prolonged this irritation, the more likely is it to lead to epithelioma. Thus :—

2. Poor people who keep their quid of betel in the mouth for a long time (sometimes all night) are more prone to cancer of the mouth than are those who can afford to change the betel-nut at frequent intervals.

3. Vitamin-A deficiency is an aetiological factor, the disease being most common in those areas where diet is most deficient in vitamin A (McCarrison, 1931).

4. The use of lime made from shells is more injurious than is lime made from limestone, owing to its fine division and rapid setting free of the alkaloids from the tobacco. Hence the high incidence of cancer of the mouth in the districts near the sea coast where shell-lime is used.

5. Cancer of the mouth is common only in Travancore, Madras Presidency, and Ceylon, the three areas of India where tobacco is used with the betel leaf. Certain kinds of tobacco, notably the strong Vadakkan tobacco of South India, and the tobacco of Jaffna, Ceylon, are more prone to cause cancer of the mouth than are the milder tobaccos such as those grown around Madura. (*See also* Snijders and Straub, 1923.)

6. The betel leaf and areca nut are in themselves harmless in this respect. So is the tobacco unless mixed with lime. Orr sums up his results in the following paragraph, taken from the annual report for Neyyoor Hospital in 1936 :—

" Cancer of the mouth is still and probably always will be our really characteristic indigenous disease in Travancore. If the Government were to put an embargo, or a very high duty, on certain kinds—two only—of tobacco, we believe they could cut out with a stroke of the pen some 70 per cent of the cancer in this country. But as the research which has resulted in this finding was performed in a Mission and not a Government institution, it is unlikely that it will be accepted as authoritative in India. Be that as it may, the fact remains that over 500 of our operations each year are for the relief of cancer of the mouth, tongue, jaw, and cheek. And 90 per cent of the disease arises from chewing two kinds of tobacco with the betel nut. The other four or five kinds which are used locally seem to have little or no deleterious effect." Since this was written we have done some 800 operations every year for carcinoma of the mouth, and we have seen no reason to alter or to modify the above conclusions during the ten years that have elapsed since 1933, when this investigation was made.

The aim of the present article, however, is not to discuss the aetiology of this disease, but its treatment. In the course of the last twenty years we have been led gradually to see what is in all probability the best treatment for any particular class of case. In many this is by operation; some are best dealt with by electro-coagulation with diathermy; many require radium; a few should be treated by deep X-ray therapy; and a good number require a combination of two or more of these lines of treatment. As there must be very few hospitals of this size in the world where so many cases of buccal cancer are seen or dealt with, I venture to submit to my fellow surgeons some of the more important points in technique of operation, radium application, etc.,

which we have found out or evolved during these twenty years. We have likewise seen many of the limitations of the various methods of treatment, and have seen disasters, too, both in our own cases and in those of other clinics where the treatment has been wrongly applied.

The work of a hospital in a country district in India suffers from one great drawback, of special importance in dealing with malignant disease. It is almost impossible to follow up cases as we should like to do. Many recurrences go straight to other doctors or hospitals, and we never hear of them again. Many go to quacks and rapidly die under their hands—and we know nothing of their fate. On the other hand, we are constantly seeing the failures of other surgeons and clinics, and a great many of the recurrences we see are from other hospitals. Anything in the nature of complete statistics of our cases is therefore out of the question. We do, however, keep in touch with a certain number of our cases, and we see them often, years afterwards, when they come bringing some other patient for our treatment.

But after all these years, one can at least feel that one has a fairly good idea as to what is the rate of recurrence of each class of case, and one learns in a general way, not by keeping records of figures, what is the relative value of radium, operation, X rays, and their combination, in dealing with these cases. This paper, then, will not be burdened with figures. But of more real value, I maintain, than any set of figures are the general impressions one has obtained, and the improvements in technique of operative methods which we have found out and evolved in the course of dealing with so many cases of cancer of the mouth. Experience rather than statistics, then, must be the foundation of these remarks.

THE TREATMENT OF BUCCAL CARCINOMA

The habit of chewing betel nut and tucking the quid into the cheek should, we might suppose, affect the cheek and the gums in almost equal proportion. But such is not the case; the gums seem to be more resistant to cancer-producing irritation, so that the greater proportion of our cases begin to show malignancy on the cheek. From the cheek the growth, if neglected (or treated by quack 'physicians', as is the case with most of our patients), spreads in a few weeks to one or both jaws. From the tongue such spread is far more rare, the growth being confined to the tongue itself until a very late stage is reached.

1. Cheek and Lips.—In general, it may be said that growths of the cheek are fairly sensitive to radium, except when they are very superficial and of the leukoplakic type. The softer and more fleshy the growth, the more successful is radium likely to be. The harder and more approaching to leukoplakia is the growth, the less effective is radium. For this latter type of growth, we employ an excision with diathermy, followed at once by the insertion of radium needles around the edge of the growth, a few milligrammes of radium being inserted in the intervening space originally occupied by the growth.

Leukoplakia of the cheek, especially if the Kahn test be negative, is to be looked upon with grave suspicion (Lane Claypon, 1930; Cheatle, 1930). Such cases we invariably treat with diathermy, sometimes also using radium as just described. Leukoplakia of the tongue, however, only appears to become malignant if it is of a very thick and dense type. Stewart (1931) considers that all leukoplakia of the tongue is potentially cancerous, with which I agree; but I should not subject the more harmless looking leukoplakias of the tongue to diathermy if there was the probability of keeping in touch with the patient; the thick variety, however, calls for diathermy and radium, or at least for a biopsy before it is considered safe to leave it.

When radium therapy is given, the dangerous and unknown growing edge is first dealt with, and the intervening space, radiated in part by the cross-fire of the surrounding needles, may require only a few milligrammes of radium. In general, it may be said that radium needles of 1 cm. active length each containing 1 mg. of radium element, if placed 1 cm. apart, should be in a cheek for 10 days. That is to say, each cubic centimetre of epithelioma requires approximately 250 mg.-hr. of radium. This is not a strictly accurate statement, and I prefer personally not to talk or think in 'milligramme-hours'; for double the strength of radium mentioned (i.e., 2 mg. per 1 c.c. active length of needle) has much the same effect in 4 days as the single mg. needles have in 10 days. A 5-mg. needle of 3 cm. active length is just about twice as effective as a 3-mg. needle of the same length. For a soft growth in the tongue or lip or any fungating growth, 1 mg. radium per 1 c.c. of tissue is effective in about 8 days. It is advisable always to add 20 or 25 per cent to the estimated amount of radium, in case of irregularities in the distribution of the needles, or unexpected radio-resistance of the tissue. It is of supreme importance that underdosage of radium should never on any account be given.

Large, fungating growths of cheek or lip can have the fungating part removed by the diathermy knife, in order to save radium, which is used for the non-projecting part of the growth and the tissue immediately around its edge. This method leads to a worse cosmetic result than the use of radium for the entire growth. Some of the normal tissue is destroyed by the diathermy which radium, used alone, would preserve. But by this method more radium is available for the other cases waiting for it in hospital; in our fight with grim death we cannot often think too much of cosmetic results.

It will be noted that in this paper radium is always mentioned as 'inserted' in the form of needles. Considerations have led us to adopt this method of radium treatment almost to the exclusion of all others.

The removal of glands must be done in every case. Glands are always dealt with by operation, though occasionally with the employment of radium as well—i.e., in conjunction with operation, and as a reinforcement to it.

Where cancer of the cheek is very near to the bone of either jaw, radium will very often have to be inserted close to the bone, and a sequestrum will later be formed in some cases, the superficial layer of the bone being killed by the radium.

The extraction of the teeth contiguous to the growth should be done at the same time as the removal of the glands. It should never be done beforehand, or even at the time of insertion of the radium, for cancer cells may become implanted in the sockets of the teeth, and lead to a carcinoma of the jaw some months later. Twenty years ago, when fresh from the teaching hospitals of England, I used to remove teeth in order to clean up the mouth for subsequent surgical procedures; but so often did I notice the occurrence of this implantation-cancer of the jaws, that I gave it up, and never practise it now, however dirty and septic the teeth may be. The teeth are painted over with several coats of iodine, just before operation.

The prognosis of radium-treated carcinomata of the cheek is very good, so long as radiation is sufficient. A small radium burn is not of serious import, and can be treated later by diathermy. Under-radiation, on the other hand, is certain to be followed by recurrence, and the recurrence may be resistant to radium treatment.

Two or three weeks after treatment, the cheek must be examined, and the presence of a superficial ulcer of smooth, wash-leathery appearance extending over the whole of the area originally occupied by the growth (and a little beyond it) means that treatment has been adequate. It is partly in order to keep the patient long enough for this to be observed that I invariably operate upon the glands after, and not before, the growth has been dealt with. The other reason for this is that if the glands draining a cheek are removed before the growth is dealt with, the lymphatic drainage of that cheek will be diverted into new channels, such as to the pre-auricular gland on the same side, or the submaxillary group on the *other* side, and secondary growths may appear in these situations later.

2. Lower Jaw.—The lower jaw is but seldom suitable for the use of radium. Occasionally in patients who have refused operation but submitted to radium treatment, I have been constrained to use radium. But the result has always been the same. If the cancer is destroyed by the radium, the jaw will also have been destroyed, and eventually, perhaps months later, will have to be removed. I remember a tragic case of a fine-looking man who implored me to radiate his lower jaw, and not to operate upon it. I did so, and the cancer disappeared. But the jaw started necrosing, and a few months later had to be removed. The patient stood this operation well, but developed an abscess of the lung, from which he eventually died. Patients with cancer of the mouth stand one or two anæsthetics well, but not many more, and those requiring a series of operations (such as plastics, etc.) very often develop abscess of the lung after their fourth or fifth operation. For this reason it is my rule to do everything possible in one single operation, and to remove in one block the half-jaw including its condyle, submental and submaxillary glands with the salivary submaxillary, and the large upper deep cervical gland usually known as the tonsillar gland. In most cases this will be sufficient to 'cure' the case—a word I hate to use about cancer, but it will be obvious what is meant. If there be any involvement even of one single deep cervical gland, the case should later have a complete block dissection of the deep cervical area, with part of the sternomastoid muscle and the anterior and posterior cervical glands. The jugular vein can nearly always be preserved, and this should be done, for its removal leads to cerebral congestion in a certain proportion of cases, many of which eventually die from it a few days after operation. If the vein has been adherent to the glands, a few radium needles should be inserted alongside it at that place immediately the operation is finished and before the skin is sutured.

With regard to the anæsthetic to be employed, we have found in South India that chloroform on an open mask is a very safe anæsthetic. In the warm climate, a fair amount of chloroform evaporates into the air, giving a greater margin of safety. In many thousands of cases anæsthetized by open chloroform at this hospital, we have had practically no deaths from overdose or in other ways directly attributable to the anæsthetic. The feeding up of patients before operation, and the administration of an ounce of sugar with 60 gr. of sod. bicarb. a couple of hours before the anæsthetic is given, has entirely eliminated the danger, at one time so real, of post-chloroform acidosis. Moreover, when a laryngotomy is performed, chloroform can be so easily administered by a Junker bottle. So it has come to be our anæsthetic of choice. We have experimented with other anæsthetics for jaw cases, especially with the two following:—

a. Basal paraldehyde by the rectum, with injection of novocain into the foramen ovale and complete local block anæsthesia, is theoretically sound, though laryngotomy is distressing to a conscious or half-conscious patient, and without it the difficulty and danger of the operation of excision of the jaw are materially increased. We occasionally give this method of anæsthesia in cases such as diabetics or 'chesty' individuals who are unsuitable for chloroform. In a series of 100 lower-jaw excisions anæsthetized by this method, we found no improvement in our mortality or morbidity figures as against simple chloroform.

b. Rectal ether in olive oil, with or without local novocain, has its advantages, but it, too, seems to produce lung complications as frequently as chloroform. We did a series of over 150 with rectal ether; and other methods have been tried, but we have not found that our mortality, immediate or remote, is materially cut down by any particular method. Even in the best hands, the excision of the lower jaw is a severe operation, performed as it usually is on old people with oral sepsis; whatever be the method of anæsthesia, a surgeon must be thankful, and so must his patients, if less than 10 per cent mortality results from the operation.

Immediately the patient is sufficiently under to lose reflexes, laryngotomy is performed, and the throat is packed with gauze; a single swab about 4 in. × 8 in. of 16 thicknesses of gauze is usually sufficient. The laryngotomy tube is left in, at the discretion of the nurse in charge of the case, for one or more days (not more than four) after the operation.

3. Tongue.—The tongue exhibits a greater variety of lesions of the epitheliomatous type than do the cheek and jaws. Each variety has its own special methods of treatment, but on the whole it may be said that every case of cancer of the tongue is best treated by the insertion of radium needles, though in a few situations operation is required as well.

a. Side of the Tongue.—This is the most usual site for carcinoma, and is nearly always the easiest site to treat. Radium needles are inserted in pairs. I use a 4-cm. needle of 2-mg. strength, active length 3 cm., inserted into the front of the tongue, and anchored there by being tied to a 1-in. (2½-cm.) needle of 1-mg. strength and active length 1½ cm., inserted into the back of the tongue. As many pairs of needles as are required by the size of the growth are inserted in this way, as shown in the figure (*Fig.* 24). If the radium

FIG. 24.—Radium needles inserted in pairs into tongue.

available admits of only 1 mg. of radium element per 1 c.c. of cancer tissue, the needles will have to be left in for ten days. Double this strength, however, for half the time, is preferable. Most of the needles are inserted at the border of the palpable growth, or just outside it; a few may have to be inserted into the substance of the growth, in which case precaution must be taken that their points do not penetrate beyond the growth into normal tissue. The threads of the radium needles are anchored by a stitch of strong catgut inserted into normal tissue near the tip of the tongue, and made to pass through a rubber tube, to prevent the patient from biting them off; they are all further fixed by a stitch of strong thread to the cheek.

If the growth is entirely confined to the one side of the tongue, a unilateral block dissection of submental (bilateral), submaxillary, and deep cervical glands, as far down as 2 cm. below the omohyoid muscle, is sufficient. The glands of the posterior triangle need not be removed unless there is involvement of any of the glands beneath the sternomastoid muscle. Observation must be kept on the glands of the other side; if any of them become involved, operation combined with implantation of blunt-pointed radium needles around the main vessels is usually the treatment of choice.

I am not in favour of subjecting the glands in tongue cases to X-ray therapy except when they are fixed, or when the carotid artery seems to be adherent to the growth or involved in it. The effect of deep X rays on the patient's physical and psychological condition is sometimes very sinister.

b. Tip of the Tongue.—This is hard to radiate well, and a carcinoma involving only the tip is best removed with diathermy, with radiation of the base of the wound with short needles inserted transversely.

c. Back of the Tongue.—This may be the seat of a large, soft growth, which sometimes extends down to the epiglottis. This type of growth is very radio-sensitive, but if it is very soft it is difficult to persuade radium needles to remain in it for long, and longish needles with high dosage for a short time is the ideal treatment. These carcinomata must be dealt with very gently; small fragments of the growth, if they should be inhaled, will produce secondary growths in the lung, a type of growth which is not treatable by deep X rays with much hope of success. Radical removal of glands on both sides must be carried out. Note that long radium needles can be inserted into the back of the tongue from just below the mandible, between the facial artery and the angle of the jaw.

d. Floor of the Mouth.—This is often involved in tongue cancer, and radium can be inserted both within the mouth, parallel to the long axis of the tongue, and from without, just inside the edge of the mandible. These needles should point vertically upwards. Some sequestration of the inner surfaces of the mandible may very probably occur. The deep cervical glands are removed later; the glands of the submaxillary and submental groups will probably have been adequately radiated by the needles put in from outside, but if any doubt is felt about this, they should, of course, be removed. After the radium needles have been taken out, small incisions below the mandible for drainage may have to be made, for infection of the submaxillary spaces is almost bound to have occurred.

e. Epiglottis and Extreme Back of Tongue.—This is a difficult situation to treat; radium needles inserted from without, near the angle of the jaw, offer the best chance of cure. The upper deep cervical glands, including those beneath and behind the mastoid process, are apt to be involved early, and sometimes the carotid artery is found to be adherent to the glands. Thus, in these cases, deep X-ray therapy may be indicated. The danger of removing such glands, combined with the use of radium, is twofold—infection of the carotid sheath, leading to mediastinitis; and secondary hæmorrhage from the carotid artery.

f. Tonsil Region.—Unless the growth is reported early, the tonsil is a dangerous site for carcinoma or sarcoma. As in the case of the epiglottis, the deep glands are likely to be involved at an early stage, so that there may be a cancerous block of tissue including tonsil, glands, and the main vessels. Deep X-ray therapy, combined with the radiation by insertion of long radium needles into the deeper parts of the growth, and into the tonsil itself, offers a chance of cure. X rays of 400 kv. and over are necessary for this type of case; a smaller voltage will not suffice to penetrate the deeper regions of the mass of growth. It is only in early cases that the insertion of radium needles into the growth, and operation on the glands, is a proper form of treatment. I have done two cases of this nature with successful results for two years at least, using only radium for both growth and glands. For carcinoma of the tonsil, long radium needles can often be satisfactorily inserted into the tonsillar region from without, just in front of the ramus of the mandible, pushed well in beneath the mucous membrane and the anterior pillar of the fauces until their active part reaches the tonsil.

g. Whole Tongue.—When the tongue is badly involved in carcinoma, so that it is fixed, and cannot be protruded, it is usually best to remove the whole tongue, after a preliminary laryngotomy. Some growth will usually be left, or at least suspected, in the floor of the mouth, and the whole of this region is treated at once with radium, inserted from outside, in the submental and submaxillary areas. These cases if thus dealt with often do surprisingly well. Glands must, of course, be removed radically on both sides, and care must be taken to preserve at least one, if not both, the jugular veins. For this purpose a combination of operation and radium treatment is necessary.

General Principles.—It is important to avoid whenever possible the insertion of two or more separate lots of radium.

The first insertion may produce radio-resistance to an extent which cannot be gauged; the dosage for the second insertion is then almost impossible to guess accurately. Complete treatment by one insertion of radium, combined if necessary (as in the case of the whole tongue) with operation, must be done at one sitting if possible. The tongue stands both radium and diathermy well, and growths in its substance are usually very radiosensitive. A hard, leukoplakic growth, however, is best removed by diathermy, as in the case of the cheek. Radium is then inserted in the bed of the growth, as a safeguard, at the same sitting. Radium burns must be treated; in every case a biopsy is required to make sure they *are* radium burns, and not recurrences; burns are treated by cautery with the diathermy—this also produces a burn, but one which heals well, and is much less painful than is the average radium burn.

4. Upper Jaw.—When this is involved in cancer spreading from the cheek, the alveolar and palatal part of the jaw is usually affected; the antrum is often free from growth, and the orbital floor is quite uninvolved. In these cases, the jaw should be removed by operation.

5. Glands.—If the growth and glands cannot be removed at the same time, it is a sound general principle to operate on the glands only after the growth has been either removed or rendered innocuous by radium.

There is a risk, of course, of the patient running away before the glands are dealt with; but that can often be avoided by pretending that an anæsthetic is necessary for the extraction of the radium needles, or by keeping the patient unnecessarily in bed. The greater risk is run by dealing with the glands before the growth is operated upon; the growth, being still active and in situ, develops new lymphatic drainage, and may involve a new group of glands. For instance, a cancer of the cheek normally involves the submental and submaxillary glands; if these are removed lymphatic drainage is diverted to the pre-auricular gland, the lymphatic gland in the lower pole of the parotid, and even to the submaxillary glands on the other side or the deep cervical group on either side.

During the first few years of my life in India I used to operate on the glands before the growth; but this transference of the drainage to other groups of glands, and the appearance of cancer in them, occurred so often that I soon gave it up, and I never do it now except under strong indications.

With regard to the question of which glands should be removed, this depends, of course, to some extent on their involvement. Cancer of the cheek region, including lips and jaws, tends first to involve the submental and submaxillary groups, and an isolated gland near the common facial vein. Very occasionally the tonsillar glands in the upper deep cervical group are involved. Beyond the glands mentioned there is a layer of fascia which, though in places very thin, acts as a boundary for sepsis; it is safe to remove all these glands in a lower-jaw operation, without risking infection of the carotid sheath and its serious sequel of anterior mediastinitis.

In the cheek, lip, or jaw case in which there is no palpable enlargement of any glands at all, it is sufficient to remove this group. In an early

cheek case I remove only the submaxillary and submental glands, but always at least these two groups, the submental group being dissected out with the diathermy knife. If there is involvement of only a few of the submental or submaxillary glands, the upper deep cervical glands must also be removed, and the case must be kept under observation. A complete block dissection of the neck is a risky operation to a patient who is either septic or debilitated by a previous removal of a lower jaw, and the relative risk of leaving the glands behind, and of subjecting the patient to a ¾-hour anæsthetic or a risk of mediastinitis must be weighed. Radium can sometimes be used to attack these glands if a block dissection is considered too dangerous.

In the case of the tongue, a relatively much more extensive gland operation must be done. As a routine, if no palpable involvement of glands can be made out, and the cancer is of fairly small size and confined to one side of the tongue, I make a practice of removing submental, submaxillary, and deep cervical (anterior) glands down to the omohyoid muscle. If at operation any of these are found to be involved, the operation is extended. The incision is extended down to the clavicle (*Fig.* 25, A) over the sternomastoid muscle; this muscle is defined front and back, isolated from the jugular vein in the middle third, and divided just below the spinal accessory nerve. The two halves are retracted up and down, and an excellent view of the glands beneath it is obtained. These are all removed, together with adherent muscle or vein. The vein is only removed if its compression produces no symptoms and if it is really adherent to glands. It is safer to leave it behind if it is very large, and to peel the glands off it, leaving radium needles along its length of a suitable dose, usually about 14 mg. for eight days. If any single deep cervical gland is found to be enlarged and obviously malignant, a complete removal of all deep and posterior cervical glands should be done. An extension of the incision over the brachial plexus region (*Fig.* 25, B) may be required.

In a lower-jaw case this extensive removal, if found to be necessary, should only be done when the jaw operation has healed sufficiently well to render the danger of sepsis in the carotid sheath fairly remote; drainage of the lower end of the wound is necessary for a few days, in case any sepsis should occur, and to prevent mediastinitis.

The upper jaw drains into the pre-auricular, parotid, buccal, and submaxillary glands and only these glands need be removed unless any involvement of them indicates that a wider removal is advisable. These cases must always, if possible, be observed at least once a month for six months, and thereafter once every two or three months for two years.

6. Carcinoma in Certain Special Situations.—

a. Involvement of the lower jaw with a very extensive carcinoma of the cheek indicates a preliminary radiation of the cheek and upper part of the growth, and removal of the lower jaw by operation. Conversely, an operable upper jaw

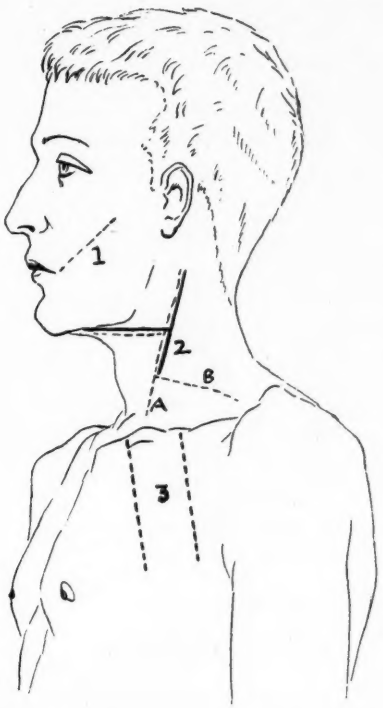

FIG. 25.—Incisions for: (1) Upper jaw, alveolar part; (2) Glands of neck, upper glands only, A and B being extensions; (3) Tube flap.

combined with a fairly extensive carcinoma of the cheek demands radiation of the cheek and removal by operation of the upper jaw.*

b. Carcinomata in the *angle between the jaws* is best treated by radium at first; the lower jaw, if necrotic, may have to be removed at a later date.

c. Carcinoma of the *tonsil* is the most fatal of all buccal carcinomata, owing to its early involvement of the deepest cervical glands.

d. Carcinoma of the *epiglottis*, another very fatal variety.

e. Carcinoma of the back of the *nasopharynx* and ethmoid region is very rare. I have only seen 6 cases. It is best treated by radium. If the extent of the growth is doubtful, a partial excision of the upper jaw may be advisable in order to carry out thorough observations of the growth, which is particularly liable to escape thorough radiation if care is not taken. Of 2 cases I radiated without operation, both died. One case which I treated with radium had had deep X-ray therapy one year previously in Madras; she died 2 years after beginning of

* In both these cases, the upper incision of the lower-jaw operation or the lower incision of an upper-jaw operation has to be made boldly through radiated growth.

treatment. Three cases were treated with radium insertion after partial excision of the upper jaw. One is alive 10 years after operation; of the others one is untraced and one is alive 3 years after operation.

Though this is but a small number of cases on which to base dogmatic statements, the results are sufficiently definite to make me feel that in carcinoma of the nasopharynx the routine treatment should be by radium after excision of the hard palate on one side, with the alveolar part of the jaw, leaving the orbital floor and the anterior wall of the antrum, but removing the inner wall of the antrum and the lower turbinate. This enables excellent observation of the growth to be made throughout its treatment and after. Recurrences are thus "caught in time", and a dental prosthesis filling in the gap in the palate and the alveolar portion of the jaw can be supplied a year or so after the operation. This can be removed as often as is required for observation of the site of the growth. A few days after the excision, radium needles can be applied, under direct observation, to the growth.

Plastic Operations.—Many cases of cancer starting in the cheek will require removal of a large piece of the cheek, leaving a gap; in lower-jaw cases especially is this frequently necessary. After the wound has attained a healing condition, i.e., when the size of the inevitable gap is apparent, plans must be made for its closure by plastic operations. The inner side of the cheek must be formed either by mucous membrane or by skin. In women, this skin can often be supplied by turning in flaps from the edge of the gap, or by a sliding flap. In men this is rarely possible on account of the hair on the skin, and for most male and some female cases a tube-flap from the chest is necessary. The base of the tube is best at the clavicle; the distal end should lead to hairless skin between the nipple and the axilla; the two incisions isolating the tube must provide a good tube, and must therefore be in no place less than 2 in. apart. (*Fig.* 25, 3.)

Mortality (*Table III*).—In this series of cases it must be remembered that many hundreds of cases have been dealt with which I was brought up in London to consider inoperable. The death from cancer of the mouth is so horrible that many patients ask me to operate on them "even if it will kill me", and if thus invited to do so, I usually obey the call of humanity and neglect that of statistics. The appended table shows the mortality of the various types of epithelioma mentioned in these pages, the cause of death being hardly ever operative shock, but nearly always pneumonia, abscess of the lung, or congestion of the brain following ablation of the internal jugular vein.

Table III.—Table of Mortality of Operations for Cancer, 1923–1942

Site of Growth	No. Operated	Deaths While in Hospital*	Percentage	Remarks on Chief Cause of Death
Cheek and lips	2533	5	0·2	—
Tongue	633	12	2·0	Pneumonia
Upper jaw	349	12	3·4	Secondary hæmorrhage and pneumonia
Lower jaw	1338	114	8·5	Pneumonia, abscess of lung
Glands in neck	2590	13	0·5	Cerebral congestion
Plastic operations, etc.	996	2	0·2	Abscess of lung
Situations other than Mouth:—				
Breast and glands	113	3	3·0	—
Penis and glands	171	2	1·3	Secondary hæmorrhage, femoral
Rectum	48	4	8·3	Operation shock or sepsis
Larynx and pharynx	62	4	6·5	Mediastinitis
Cervix (mostly radium cases)	558	11	2·0	Mortality confined to hysterectomy cases. No deaths from radium treatment alone

* Includes deaths as an immediate result of operation, or during the first few weeks after operation. The large majority of the deaths except in the rectum cases fall into the latter category.

Radium versus X Rays and Operation.—I have seen so many tragedies caused by the treatment of cancer of the mouth with X rays that I am very doubtful of the advisability of treating any case of carcinoma of the buccal and nasopharyngeal cavities with X rays. Nearly every one of the cases I have been personally in touch with which have been treated by deep X-ray therapy have eventually had a recurrence of the growth either locally or secondarily, or have had insufficient radiation of some part or other of growth or glands. In addition to this, X-ray therapy always has some ill effects on the general health of the patient, and these effects may be profound in some cases, reducing them to a condition in which they cannot stand the further treatment, perhaps involving anæsthesia for radium or operations, which may be necessary for their cure.

The ability of X rays and radium to cause the start of a new growth if a certain dosage be given is also a factor to be considered. These secondary new growths develop only in certain few individuals, as a response to a dose of X rays or radium which probably varies with the individual. In cases of carcinoma of the cheek or tongue which have been treated with radium of correct dosage, by insertion of needles, I have noticed that carcinoma, if it develops in this way, starts

approximately 4 to 5 cm. from the edge of the radiated primary growth, at least six months after the radiation is done. It appears to occur in this way in only 1 per cent or less of cases.

On the whole, I would appeal for operation to be the normal recognized treatment for all cases of carcinoma of upper and lower jaws. Radium is the best treatment for cancer of tongue or cheek, in conjunction, as already mentioned, with diathermy or operative removal of certain types of growth such as large fungating growths, cancer of the whole tongue, and epithelioma of the leukoplakic type in tongue or cheek.

A Final Word.—Operation has not the unpleasant after-effects of radiation, and is always the method of choice except for tongue, cheek, tonsil, and a few special situations. An operation which is felt during its course to be insufficient can always be reinforced by radium. Deep X-ray therapy is very disappointing in mouth cases. Radium when used must be used in sufficient doses. Just as in the political sphere, so in dealing with cancer, whether by radium or operation, it must always be remembered that error on the side of radicality is always safer than error on the conservative side. One cancer cell left behind will kill the patient; a small radium burn or a little extra mutilation may mean inconvenience, but may mean a life saved.

Another point I would stress is this: All surgeons who operate upon cancer patients should be conversant with the practice and principles of radium treatment. I deplore the separation of so-called 'radium' clinics or institutes from the surgical side in general hospitals. The radium expert and the surgeon should work hand in hand, and the former should always be prepared to make some radium needles available for the surgeon to use at the time of operation if necessary, especially in cases of cancer of the jaws. It is hard to remember a week or two later exactly what parts of the operation area needed reinforcement with radium; it is easy to insert a suitable dose of radium exactly where it is wanted while the case is still on the operating table.

Finally, I feel that we should always remember that out duty is to relieve suffering, and often we ought to put that before the actual saving of life. If euthanasia is to be the probable effect of an operation, it may be the right thing to do it, and is in my opinion, always better than insufficiency or neglect. Perhaps that consideration may make our operations more radical and more effective. There is no excuse for a surgeon who does a shoddy or insufficient operation for malignant disease, least of all in a hospital where radium is available to reinforce operative deficiencies. "He's had about enough; we had better leave that little bit", said with the kindest of motives, in order to save an extra 2 per cent of risk of mortality, may mean the death sentence of the patient.

SUMMARY

A series of nearly 5000 cases of carcinoma of the mouth and jaws, involving over 8000 operations, is reviewed mainly in the light of answering the question: "What is the treatment of choice, operation, X rays, or radium?"

Operative technique based on over a thousand personal cases of operations for carcinoma of mandible and maxilla is described.

The treatment most suited to various groups of cases is discussed with reference to epithelioma of (1) cheek, (2) lower jaw, (3) tongue, (4) upper jaw, (5) glands of the neck, (6) certain special situations.

A brief description is given of some plastic operations essential for the filling up of facial defects left from cancer operations.

The relative value in buccal carcinoma of X rays, radium, and operation is assessed.

An appeal is made to surgeons to co-operate much more intimately with radium departments than is usually the case.

In the writing of this paper I acknowledge with thanks the permission of the editors of the *Indian Journal of Surgery*, who allowed me to quote freely from an article on this subject which I recently published in that journal (1943). I wish to thank also my colleagues on the medical and nursing staff of the Neyyoor Hospital, whose co-operation in the treatment of cancer has saved so many lives, and continues to do so. In particular I may mention Dr. I. M. Orr, my collaborator for nine years, whose researches on the aetiology of this type of cancer have been quoted; my colleague, Dr. N. E. James, who is at present in charge of our male cancer wards, and who has helped with suggestions; and Mr. Rajiah, who has copied my original drawings in a form suitable for reproduction.

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INJURIES OF THE URINARY BLADDER*

By J. COSBIE ROSS, Liverpool

Cui persecta vesica . . . lethale est.—Hippocrates.

The gloomy prediction of the Father of Medicine has thrown a dark shadow over the subject of injured bladder throughout the centuries, and this shadow has persisted up to the present time.

Injury of the bladder is not a common condition in civilian emergency surgery, but the incidence rises as a result of the numerous penetrating wounds of modern warfare. The short series of cases described below occurred within a brief period, and each case was a classical example. A further point of interest lies in the fact that there were no deaths. This sharply contradicts the view of writers previous to the Great War of 1914–18, who considered that any abdominal injury subjected to operation died; and also that of the older writers who thought that no case of rupture of the bladder ever recovered. In a series of 965 cases of abdominal injury sustained in the last war, and analysed by Wallace (1917), the bladder was injured on 45 occasions, or 4·66 per cent. Fullerton (1918) was only able to collect a series of 53 cases.

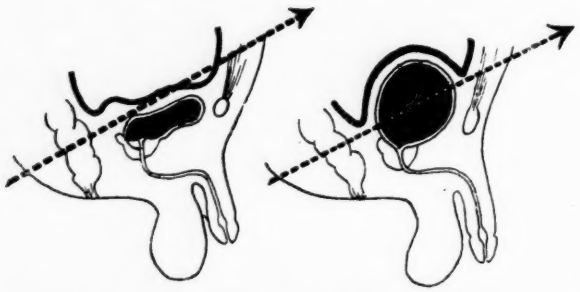

Fig. 26.—Illustrating the vulnerability of the distended bladder.

Civil injuries are dealt with at some length by American authors, who all emphasize the rise of incidence due to automobile accidents. Cahill (1937) records 20 bladder injuries in a series of 9900 consecutive urological cases admitted to his hospital; and of 74 individuals suffering from injuries of the urinary tract, Marquardt and Cook (1940) found 19 per cent involved the bladder. In discussing 53 cases of subcutaneous injury of the abdominal contents, W. E. Cody (1939) reported that rupture of the bladder occurred in 5 instances, compared with rupture of liver 12 cases, rupture of spleen 11 cases, rupture of kidney 9 cases, and laceration of renal vessels 1 case.

As might be expected, fracture of the pelvis is also present in the great majority of bladder injuries. Of a series of 60 cases no less than 40 had an accompanying fracture of the pelvis, and Tanton (1918), quoted by McAlpine, found only 55 uncomplicated cases against 312 in which fracture of the pelvis was also present.

State of the Bladder.—A full bladder is undoubtedly more prone to injury than one lying empty deep down in the pelvis. Larrey (1829), who as Napoleon's surgeon-general must have had a wide experience of wounds, pointed out this fact over a century ago.

A full bladder presents a larger target than the empty organ, and if projecting above the pubis may be injured by a penetrating wound without damage to the bony pelvis (*Fig.* 26).

TYPES OF INJURY

The three main injuries are contusions, wounds, and rupture (Hinman, 1935).

1. Contusion.—This is rare and is difficult to recognize. It is usually due to a prolonged and difficult labour, produces injury of the trigonal muscle, and may eventually predispose to the formation of a cystocele.

2. Wounds.—These are generally of military origin and frequently of the penetrating type, although an occasional case of injury of the bladder during hysterectomy, especially vaginal hysterectomy, has been recorded. A punctured wound may temporarily seal itself off as bullets tend to split the muscular fasciculi. Of Fullerton's 53 cases, in 4 cases wounds were situated in the suprapubic area, in 34 the wound of entry was in the region of the buttock, and in 5 the exit was similarly situated. Thus, in 39 out of 53 cases (75 per cent), a wound communicating with the bladder was found in the buttock area.

In many instances the foreign body is retained, and in 10 out of the 53 cases was found in the bladder.

3. Rupture.—Inebriation is a well-known predisposing cause when combined with a sharp blow on the hypogastrium. Not only is the bladder overdistended, but the abdominal musculature is not on guard. This is well illustrated by *Case* 2 of the series. Apart from this, rarer causes are :—

a. Rupture during parturition.

b. Overdistension during cystoscopy.

c. Injury by lithotrite, by excessively deep diathermy, or by the resectoscope.

d. Spontaneous rupture of a distended diseased bladder. (Crosbie, 1924.)

e. Spontaneous rupture of a normal though distended bladder (Barnes and Steele, 1935; Chisholm and Ferguson, 1939; E. H. Fenwick, 1886).

* Hunterian lecture, Royal College of Surgeons, April, 1943.

f. Secondary to osteomyelitis of the pelvis.

g. Secondary to stricture of the urethra (Keen and Goldschlager, 1938).

h. Secondary to manipulation for fractured pelvis (Cahill, 1937).

i. Trivial falls, lifting strains, or muscular exertion.

Stirling (1936) points out that a blow on the abdominal wall may cause an extraperitoneal rupture, the bladder bursting posteriorly if partly filled; if the bladder is very full an intraperitoneal rupture occurs upwards (*Fig*. 27).

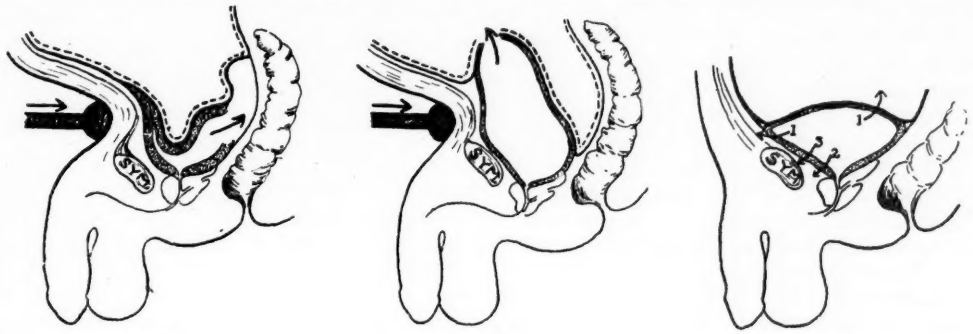

FIG. 27.—A, Extraperitoneal rupture of a partly filled bladder; B, Intraperitoneal rupture of a full bladder; C, Common sites of rupture.

In his opinion a common injury is an extraperitoneal rupture into the space of Retzius, and this is attributed to the thinning out of the muscular wall of the bladder just above the pubis (*Fig*. 28).

FIG. 28.—The thinning of the muscular wall of the bladder just above the pubis (*after Stirling*).

The writer carried out a series of experiments on the cadaver in this connexion. Unfortunately however, the factors of muscular tone of the bladder and the abdominal wall, and of rigor mortis, appeared to render the results of doubtful value. For what it is worth, overdistension of the bladder in the cadaver usually results either in an intraperitoneal rupture upwards, or an extraperitoneal leak into the space of Retzius.

CLINICAL CLASSIFICATION

This includes intraperitoneal and extraperitoneal injuries. Penetrating wounds of the abdomen usually cause intraperitoneal lesions, while missiles entering the pelvis via the buttocks, thighs, or perineum are more likely to be extraperitoneal. Intraperitoneal injuries usually affect the dome and posterior wall of the bladder and lead eventually to peritonitis. Extraperitoneal lesions are situated either anteriorly, laterally, or at the base of the bladder, and produce extravasation of urine and pelvic cellulitis.

Tanton (1918) found that extraperitoneal injuries are four times more common than intraperitoneal, whereas in civil cases Hamilton Bailey (1940) states that 80 per cent are intraperitoneal. Some authorities claim that in mining districts the percentage of extraperitoneal injuries rises with the frequency of fractures of the pelvis.

COMPLICATIONS

The majority of bladder injuries are complicated by injuries, sometimes even more serious, of other organs. Of the 45 analysed by Sir Cuthbert Wallace (1917) 25 were uncomplicated, but of Tanton's 312 cases in only 55 was the bladder the only viscus damaged.

Fullerton's 53 cases were complicated by the following additional injuries:—

	Cases
Bladder, pelvis, and rectum	11
Bladder, pelvis, rectum, and small intestine	2
Bladder and pelvis	9
Bladder and rectum	8
Bladder and small intestine	4
Bladder and pelvic colon	1

Practically all extraperitoneal injuries are associated with fracture of the pelvis, the horizontal ramus of the pubis being the part most commonly involved.

In general, intraperitoneal injuries are associated with peritonitis, and extraperitoneal with pelvic cellulitis. It has, however, been commented upon by several writers that there may be little evidence of peritonitis even after the presence of urine in the peritoneal cavity for a considerable period, e.g., three and a half days on one occasion. In practically every case of bladder injury some degree of cystitis supervenes ultimately.

Other complications include:—

1. Extravasation of urine.
2. Epididymitis. (*See Case* 1.)
3. Renal infection.

4. Osteomyelitis and necrosis of the bony pelvis. If the acetabulum is thus involved, the hip-joint may be infected.

5. Anaerobic infection, especially of the abdominal wall.

6. Secondary hæmorrhage.

7. Fæcal fistula.

8. Rectovesical fistula.

9. Intestinal obstruction.

10. Gangrene of the bladder wall (P. C. Fenwick, 1910).

PROGNOSIS

This has always been regarded as extremely grave, but it is one purpose of this paper to suggest that with modern methods of resuscitation, combined with chemotherapy, the prognosis may not be as serious as has been thought before such methods were available. In *Case* 1 the intravenous administration of plasma was particularly helpful and probably life-saving.

In uncomplicated cases the mortality has been estimated as greater than 50 per cent. The prognosis in intraperitoneal lesions is obviously graver when small intestine is involved and the "picture is dismal in the extreme; in sixteen instances there was only one recovery". (*British Official History of the Great War*, quoted by McAlpine.)

The importance of early operation is emphasized by Hamilton Bailey when discussing civil injuries. He points out that the mortality is 11 per cent if the operation is carried out within twelve hours of the injury, 55 per cent if operation is delayed for twenty-four hours, and 100 per cent if no operation is performed. It is evident, however, that the accompanying complications are also vital factors, and that their presence or absence influences the final outcome to a great extent. Again, the time factor is not always the keynote; this is well shown by *Case* 3, where operation was not carried out until several days had elapsed and pelvic cellulitis had supervened. In fact, in this case there was at first no direct evidence of injury of the bladder, and the diagnosis was not made before cystoscopy had been performed.

CLINICAL FEATURES

Intraperitoneal Injuries.—While many cases exhibit a high degree of shock, this is by no means an invariable accompaniment. The clinical features are conveniently divided into two stage :—

1. *During the first twenty hours*: Severe shock and pain are accompanied by the desire to void urine, but inability to do so. There are also symptoms of peritonism, slight generalized abdominal distension, and some degree of rigidity. Free fluid is present.

2. *After the first twenty hours have elapsed*: Signs of generalized peritonitis, and perhaps ileus, supervene.

Extraperitoneal Injuries.—Shock is not so marked, but strangury is usually a feature. It is important to distinguish this condition from rupture of the posterior urethra, when the distended bladder can be readily felt. Later, pericystitis is followed by the development of an abscess which may point in the space of Retzius. If the bladder has received an extraperitoneal injury due to a foreign body entering from the buttock, it is uncommon for the diagnosis to be clinched by the leakage of urine along the long track. On the other hand consideration of the ports of entry and exit may be helpful, and an X-ray examination is most desirable if time and the patient's condition permit.

DIAGNOSIS

American writers (Shipley and Hamrick, 1938) emphasize the importance of four cardinal features in making a diagnosis: (1) History of injury in the bladder region; (2) Presence of shock; (3) Inability to void urine; (4) Blood obtained on passing a catheter.

Stirling adds to these the presence of a 'tumour-mass' in the suprapubic region in extraperitoneal cases.

Among the various diagnostic methods advised in this connexion, the use of an intravenous pyelogram appears innocuous, and if time and facilities are available may prove very helpful, if not diagnostic. Recently, this procedure was valuable in excluding a bladder lesion in a case of abdominal injury. The suggestion that the bladder should be filled with 2 per cent sodium iodide through a catheter, and subsequently X-rayed, seems to bristle with objections. Similarly, the injection of air through a catheter for the purpose of obtaining a pneumocystogram has only to be mentioned to be condemned. These suggestions appear to be of theoretical interest rather than of practical application.

On the other hand, a plain radiograph to localize foreign bodies and to indicate fracture of the pelvis is indicated, if time, facilities, and the patient's condition permit (*see Case* 3). As in some cases the fæcal fistula, if one is present, communicates with the rectum, sigmoidoscopy may be helpful under certain circumstances.

The two diagnostic methods about which controversy has raged are catheterization and cystoscopy.

Catheterization.—McAlpine (1940) points out that the passage of a catheter will demonstrate :—

1. The patency of the urethra.

2. Perhaps distension of the bladder, and therefore no leakage (*see* below).

3. Absence of more than a drop or two of urine suggests that the bladder is perforated. An empty bladder suggests an intraperitoneal leak.

4. Perhaps pure blood or blood-stained urine.

Hamilton Bailey advises the passage of a catheter only when in the theatre, with all preparations made for the operation should this be necessary. He suggests the following technique

if blood or blood-stained urine is withdrawn: The patient is immediately placed in Fowler's position and 12 oz. of saline are introduced through the catheter; if *all* the saline is not recovered, injury of the bladder is indicated.

On the other hand, Oehlecker (1912) drew 7 litres of fluid from a catheter that had passed through the vent in the bladder into the peritoneal cavity.

Fullerton also reports a case where 30 oz. of clear urine were withdrawn through a catheter and so misled the surgeon that the diagnosis was seriously delayed.

The great danger of passing a catheter is of spreading infection, but this danger is probably outweighed by the diagnostic help obtained, especially if adequate precautions are faithfully observed.

Cystoscopy.—Opinion has been against attempting cystoscopy in these cases up to the present, but it is the present contention that if used with care cystoscopy causes no more danger than catheterization, and, as is shown in *Case* 3, sometimes the diagnosis cannot be made by any other method. In support of this may be mentioned Neligan's (1941) view that if there is reason to suppose that the damage to the bladder is extraperitoneal, cystoscopy will do no harm and may be helpful. Stevens and Dalzell (1937) state that cystoscopy will give a positive diagnosis in 85 per cent of cases, and that provided subsequent operation is prompt, it does not add to the risk.

The position may be summarized thus: if it is justifiable to insert a catheter and to inject saline, it is certainly permissible to carry out a cystoscopy, which will incidentally provide much more valuable information. It is obvious, however, that in certain cases the diagnosis will be so evident, and the condition so urgent, that these measures will be at once unnecessary and dangerous.

TREATMENT

McAlpine emphasizes four main principles of treatment: (1) Excision of wound; (2) Suture; (3) Drainage of the bladder; (4) Drainage of cellular spaces of the pelvis.

Intraperitoneal Injuries.—A midline incision is usually made, but occasionally it is possible to use the surface wound. In *Case* 1 the wound of exit was utilized. Urine and blood are either mopped up or removed by suction and the table is placed in Trendelenberg's position. The interior of the bladder must be inspected in order to exclude a retained foreign body or a second wound. Wounds of the posterior wall and dome are excised and sutured, the serous coat permitting a sound, watertight union, especially if a double row of sutures is used. Wounds deeply situated can sometimes be best dealt with from within the bladder. Other damaged abdominal viscera must be repaired, and the peritoneal cavity should be carefully closed, with or without drainage. The extraperitoneal part of the bladder is fully explored, and a suprapubic drainage tube is desirable. This is probably safer in male cases than relying entirely on an indwelling catheter.

Extraperitoneal Injuries.—It is most important to ensure that there is not also an intraperitoneal lesion. A suprapubic incision is made and the four principles enunciated above are applied. McAlpine has pointed out that the lateral walls and base are unsuitable for excision and suture owing to difficulty of access and to the perivesical fibro-fatty tissue which fixes the bladder wall. In these situations, therefore, excision may be omitted and suture alone carried out. It is especially important to institute suprapubic drainage and also drainage of the cellular spaces of the pelvis.

Fistulæ between the rectum and the bladder are favourable and tend to heal well provided cystostomy, using a wide drainage tube and not a de Pezzer catheter, is combined with a transverse colostomy. In Legueu's (1919) series of 60 bladder injuries 20 were complicated by a rectal wound, and, of these, 18 fistulæ healed within eight months of the injury.

CASE REPORTS

Case 1.—A male, aged 26 years, was admitted after having been shot by a rifle bullet, the wound of extrance being in the left buttock and the exit wound in the right iliac fossa. His admission to hospital was probably within an hour of the injury, but his condition was poor, the skin cold and clammy, and the pulse rapid, running, and almost imperceptible. As the transverse colon was lying on the abdominal wall among the pubic hairs, the rule regarding dealing with the posterior wound first was ignored on this occasion. A continuous intravenous plasma drip was started, and operation undertaken immediately as there was considerable and persistent hæmorrhage from the wound. Wound toilet was carried out as far as possible, but as the abdominal wound was extensive and there appeared to be some loss of tissue, complete excision was not attempted.

The injuries found were as follows:—

1. Multiple perforations of the small intestine, and two extensively lacerated areas of small bowel. Six perforations were sutured, and 8 in. of bowel, including the lacerated areas, were resected, and an end-to-end anastomosis performed.

2. An intraperitoneal perforation of the bladder. The fundus was extremely lacerated, the injury being represented by a gap of 2½ in. long by 1 in. wide. This wound was repaired by a double row of sutures after excision, great care being taken with the serous coat; owing to loss of tissue, it was difficult to keep the suture line sufficiently far away from the pubis.

3. Compound fracture of the right side of the pubis. Several completely detached pieces of bone were removed.

The wound was closed leaving a drainage tube leading down into the rectovesical pouch. The operation was completed by excision of the posterior wound, and by the insertion of a large-sized catheter into the urethra. Several pints of plasma and blood were given by the intravenous drip method during and after the operation. For several days intravenous

5 per cent glucose-saline was administered and a fluid intake-output chart was recorded. A course of M & B 693 was administered. Features of a stormy convalescence were :—

1. Repeated aspiration of the stomach and other measures to deal with a moderate degree of ileus.
2. Infection of the wound and fat necrosis of the subcutaneous tissues, necessitating the removal of skin sutures.
3. The development of a suprapubic fistula. This was drained by means of a gauze wick drain in a Paul's soft rubber tube.
4. Suprapubic discharge of pus, i.e., the condition described by Mathé (1940). A radiograph a month after admission revealed " some decalcification of the pubic bones on both sides adjacent to symphysis pubis. Pubis fractured, with superimposed sepsis—uniting ". No sequestrum developed from first to last.
5. The development of an ammoniacal cystitis, responding rapidly to irrigation with dilute acetic acid solution.
6. The wound eventually involved a wide area several inches in diameter and was covered by healthy granulations. A Thiersch graft was successfully applied with about 80 per cent ' take '.
7. Right-sided epididymo-orchitis, subsiding without pus formation.
8. A subacute attack of intestinal obstruction responded to the administration of prostigmine and glycerin enemata. A radiograph four months after the initial injury was reported as follows : " Stomach shows normal appearance and empties normally. Deformity of cæcum (probably due to operation). No evidence of any obstruction of the small and large bowel."

After a prolonged period the suprapubic fistula closed. Normal micturition was resumed, and the patient was discharged cured several months after the injury.

Case 2.—A female, aged 53 years, who was brought into hospital with the history of being ' beaten up ' when inebriated. Pain, tenderness, and muscular resistance were present in the hypogastric region, and there was marked tenderness in the pouch of Douglas on rectal examination. It was suggested that the patient had passed some blood in the urine. There was no evidence of fracture of the pelvis, and although the pulse-rate was 100, the temperature was normal. There was also tenderness in the right loin. The patient was taken to the theatre and cystoscopy was performed with the patient in a modified Fowler position. No more that 3 oz. of lotion were injected into the bladder, as after 2 oz. slight pain was experienced. The urine contained a fair amount of blood. Both ureteric orifices were seen and both emitted a clear efflux of urine. On the left side, near the fundus, and posterior to the air bubble, there was an irregularly bruised area largely concealed by a mass of adherent blood-clot. An intraperitoneal rupture of the bladder was diagnosed and operation carried out forthwith. A midline infra-umbilical incision was made, and the peritoneal cavity was opened and found to contain a small quantity of urine. There was a vertical slit-like intraperitoneal rupture of the bladder, the rupture being situated to the left of the midline posterior to the fundus. The rupture was about 1 in. in length and appeared to be temporarily occluded by blood-clot. The rupture was repaired by a double row of sutures, and especial care was taken with the peritoneal coat. The rest of the abdominal contents were uninjured. A drainage tube was inserted into the pouch of Douglas and brought out of the lower end of the wound, which was then closed. A large catheter was inserted into the bladder via the urethra.

Convalescence was uneventful, and healing was obtained without the development of a suprapubic fistula.

Case 3.—A male, aged 27, was admitted with a small wound of the buttock. There was no exit wound. His general condition was excellent, and as a great many serious air-raid casualties had been admitted the same night apparently little was done for him initially apart from cleaning and dressing the wound, combined with the usual injection of anti-tetanic serum. He was seen by the writer for the first time two days later, as by then an indwelling catheter had been inserted on account of severe dysuria. The urine did not contain blood. A radiograph revealed a metallic fragment in the pelvis and the buttock wound appeared unhealthy, exuding a few drops of thin fluid suggestive of urine. I explored the wound, which led down to a fracture of the lateral border of the sacrum. It appeared likely that the base of the bladder had been injured, but in view of the favourable course no more was done on that occasion apart from packing the wound with an acriflavine pack and providing free drainage. During the next few days his general condition remained *in statu quo*, and urine drained via the catheter without difficulty, but a tender swelling gradually developed on the left side of the suprapubic region. Several days after the original operation a suprapubic incision was made, evacuating thick creamy pus from the pouch of Retzius. The abscess cavity led down to the left side of the base of the bladder, but no foreign body could be felt. The bladder was not opened, and the wound was closed with a large drainage tube into the abscess cavity. When cystoscopy was performed previous to the drainage operation, 5 oz. of lotion were injected into the bladder without discomfort ; while the right side of the bladder was normal, there was much ecchymosis and œdema of the left side near the base. No definite opening could be seen, but a deeper shadow in the centre of the ecchymosed area suggested this. The foreign body was not in the cavity of the bladder. Following the operation, progress was satisfactory and the suprapubic wound healed without the development of a urinary fistula. Cystoscopy four weeks later revealed bullous œdema around the injured bladder base, and there was still congestion of the left side of the bladder wall.

When seen recently this man was carrying out heavy work and was symptomless. In this case, cystoscopy not only was necessary for diagnostic reasons, but also excluded the presence of a foreign body in the bladder, which did not require suprapubic drainage at any stage.

Case 4.—A female, aged 30 years, was punched in the lower part of the abdomen. Two hours previously the bladder had been emptied. Some abdominal pain was experienced, so she retired to bed. Several hours later the patient awoke, and on attempting to pass water, experienced severe abdominal pain and collapsed. On examination at hospital, there was lower abdominal tenderness and rigidity, and a little blood-stained urine was evacuated through a catheter. The blood was dark in colour, and did not appear fresh. There was a mild degree of shock present. An intraperitoneal rupture of the bladder was diagnosed,

and the patient taken to the theatre. Operation was performed eleven hours after the injury.

CYSTOSCOPY.—This was performed with the patient in a modified Fowler position. The cystoscope passed easily, and 9 oz. of blood-stained urine were evacuated. On injection of 2 oz. of sterile lotion pain was felt in the suprapubic region, so no more was injected. On inspection, a bruised area was seen just behind the fundus, and in the centre of this was a dark cleft, probably representing the rupture. A significant feature was the absence of the air bubble.

OPERATION.—A midline infra-umbilical incision was made, and the peritoneal cavity opened. There was some urine in the pelvis, but no peritonitis had developed. There was an intraperitoneal rupture of the bladder, a little over 1 in. in length, running vertically upwards from a point on the postero-superior aspect to the highest part of the bladder. The rupture was sutured and the urine mopped out of the pelvis. The peritoneal cavity was closed, leaving a drainage tube leading down into the pouch of Douglas, and a large Malecot catheter inserted through the urethra into the bladder.

A course of sulphathiazole was administered after the operation, and the patient was nursed in the Fowler position. The wound healed well, catheter drainage being maintained for ten days. No suprapubic fistula developed, and the patient was discharged from hospital healed within three weeks of the injury.

SUMMARY AND CONCLUSIONS

1. Injury of the bladder is not a common condition, either as a civil emergency or as a result of warfare.

2. In the majority of cases the injury of the bladder is gravely complicated by associated damage to adjacent structures.

3. An entrance or exit wound of the buttock is found in at least 75 per cent of cases. Usually through-and-through wounds are oblique in direction from the buttock to the suprapubic region or vice versa. Wounds of the buttock should, therefore, always be regarded with suspicion, especially as there may be no discharge of urine through the wound owing to the length of the track.

4. It is not always essential to drain the bladder by the suprapubic route; a large indwelling catheter may be sufficient, especially in the female.

5. It would appear that cystoscopy has a diagnostic value in this condition, and, indeed, is the only precise means of confirming certain types of injury.

6. Possibly the future will show that the prognosis, as a result of modern methods of resuscitation, combined with chemotherapy, is not as gloomy as it has been considered in the past.

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INTRAPERITONEAL CHEMOTHERAPY

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PERITONITIS has long been dreaded by surgeons as a complication of the diseases of the gastro-intestinal tract and of operative procedures in which opening the peritoneal cavity is a necessity. It is most commonly caused by a bacterial flooding of the cavity, due to perforation of some hollow viscus secondary to a disease of that viscus, and the resulting bacterial flora of the infection is therefore extremely various and often multiple in its types. Far more rarely a peritonitis results from a blood-borne infection or from a direct spread upwards by way of the female genital tract. This variety of the disease (known as primary peritonitis) is far more lethal than the secondary type and responds far less readily to any form of treatment.

For the past two or three years sulphonamide drugs have been used in the prevention and treatment of peritonitis and have been the subject of much animal experiment, especially in America. Sulphanilamide was used first by direct implantation, followed by sulphathiazole, sulphadiazine, and mixtures of these. I have practically confined my attention to sulphapyridine (M & B 693), and it is my belief that this drug possesses advantages over other sulphonamides for intraperitoneal use, but it is impossible to be dogmatic when the number of cases suitable for such treatment are limited in one man's experience. There have been few published results of intraperitoneal chemotherapy in England, beyond the excellent papers of Vaughan Hudson and his collaborators (1941 and 1942).

The bacteria most commonly responsible for 'secondary' peritonitis are the normal inhabitants of the gastro-intestinal tract—*B. coli*, various strains of streptococci, *Cl. welchii*, and *B. proteus*. *B. pyocyaneus* is a common secondary invader. *B. coli* will often outgrow other bacteria. Streptococci sometimes cause a severe peritonitis in a perforative lesion of a hollow viscus, and also produce an extremely lethal type of primary infection. Anaerobes such as *Cl. welchii* are commonly found in the peritoneal exudates after bowel rupture, but are usually swamped by the pyogenic organisms. Many cases of appendicitis with free peritoneal fluid give either a pure culture of *B. coli* or a mixed growth, usually of *B. coli* and non-hæmolytic streptococci. Mixed infections do not respond nearly so readily to sulphonamide therapy as pure ones, but owing to the non-specificity of the drugs they exercise a bacteriostatic effect of some degree on most of the bacteria occurring in a mixed infection, and herein lies one of the great advantages of this method of treatment. In primary peritonitis the usual organisms are pneumococci, streptococci, and gonococci, the pneumococci accounting for about half the cases.

It is now known that individual members of the sulphonamide group do not have a specific action on any given organism, but that organisms can be arranged in order of susceptibility to the sulphonamide group, and the sulphonamides can be arranged in order of bacteriostatic potency. It follows that an infection due to one of the less susceptible organisms, such as the staphylococcus, will be unaffected by chemotherapy unless one of the most potent drugs is used—e.g., sulphathiazole. If no substances are present which inhibit the action of the sulphonamides, then the higher the concentration of the drugs the greater will be their activity. The more organisms there are present and the higher the amount of inhibiting substances, so must the concentration of the drugs present be higher. Green and Parkin (1942) found that the antagonist of the sulphonamides is an enzyme, the substrate of which is *p*-aminobenzoic acid, and it is the capacity of the sulphonamide compound to block this substance which determines its activity. Para-aminobenzoic acid is often found in high concentrations in pus, tissue extracts, and related substances, and their presence therefore calls for a higher concentration of the chemotherapeutic drugs—a fact which is demonstrated in the local treatment of frankly purulent peritonitis, which takes far longer to clear up than the case in which little pus is present.

There is also the possibility that a sulphonamide-resistant strain of bacteria will be encountered, or that a particular strain of bacteria will become resistant in time if not quickly overcome by the drugs. Erhlich years ago pointed out in relation to the chemotherapy of protozoal infections that a large dose should be given over a short period, to prevent resistant strains developing.

ABSORPTION BY THE PERITONEAL LINING MEMBRANE

The rate of absorption of any substance placed in the peritoneal cavity is of extreme importance. The selected substance, if it is to be beneficial, must be present in a sufficient concentration in the immediate environment of the bacteria long enough either for the infection to be wiped out or for the normal body responses to be marshalled and obtain control. The ideal chemotherapeutic drug for local application will be one which has the lowest rate of absorption, thereby remaining in situ for the longest period, provided it is capable of dealing with the infecting agent and has no serious deleterious effects. There is no other method of obtaining so high a local concentration as by local implantation. If used locally either in the soft tissue or in the body cavities, a local concentration 75–100 times as great as systemic administration could give may be obtained directly at the source of infection (Mueller and Thompson, 1942).

Sulphanilamide is very rapidly absorbed into the blood-stream from the peritoneum; in fact faster than by any other route of administration (except direct intravenous injection), and so a very high blood concentration is rapidly obtained. Hudson and Smith (1942) found, using an average dose of 15 g., that a peak was reached in the blood-stream in about 12 hours, with a blood concentration of 7–12 mg. per 100 c.c., the figure falling to zero in 36–48 hours. They further noted that the concentration obtained in the blood-stream is very variable and that a peak reading of 20 mg. can be obtained and absorption continue up to three days, and that the presence or absence of inflammation does not appear appreciably to affect the absorption rate. Mueller and Thompson (1942) gave very similar figures, and also found very high levels in the peritoneal fluid taken at intervals after operation, the figures ranging from 300 mg. to 800 mg. per 100 c.c. after 40 hours. All published reports confirm this rapid absorption of sulphanilamide, and its use

may be criticized on the grounds that its rapid absorption does not allow the drug to remain in adequate concentration locally long enough for the full benefit of its direct action to be obtained, and that toxic effects are more likely to follow its use for the same reason. Jackson and Coller doubt if its local action remains very high after 1–2 hours (cf. Throckmorton's experiments with rats, in which he found no trace of the drug locally after 6–8 hours), and state that it would be ideal if some method could be devised which would slow the rapid absorption, so allowing it to remain at a high local concentration; failing that, an allied compound with a slower rate of absorption should be used. (These workers did attempt to cut down the rate of absorption of sulphanilamide by using a tragacanth suspension of the drug, but without any appreciable success.)

The absorption rate of sulphathiazole appears to lie between that of sulphanilamide and sulphapyridine, although I have been unable to find a complete series of blood-concentration figures following its intraperitoneal introduction. Lyons and Burbank (1942), in a collective review on local sulphonamide therapy, compared the properties of the various chemotherapeutic drugs, and *Table I* is reproduced from their paper. The table was deduced from a series of published experimental results by several workers following the implantation of the drugs into wounds and the peritoneal cavity. Sulphapyridine and sulphadiazine show the longest survival rates in situ, and my observation of the absorption of sulphapyridine from the peritoneum gives further proof of its long persistence locally. I have been unable to find any other reports on the absorption of sulphapyridine.

Table I.—Properties of Four Sulphonamide Drugs
(*After Lyons and Burbank*)

	Sulphanilamide	Sulphapyridine	Sulphathiazole	Sulphadiazine
Solubility in serum at 37° C.	1600 mg.	61 mg.	184 mg.	124 mg.
Persistence as crystals	6–24 hr.	7–10 days	4–5 days	5–7 days
Excretion in twenty-four hours	50 per cent	7 per cent	18 per cent	?
Persistence by chemical test	11 days	34 days	17 days	?
Diffusion time in wounds	2 hr.	24 hr.	2–6 hr.	6–24 hr.
Toxicity to cells	+	0	+	0

Table II.—Blood Concentrations of Sulphapyridine (mg. per 100 c.c.) in Five of the Control Cases after Intraperitoneal Implantation of Sulphapyridine in 4 oz. of Saline

Control Case	Hours after Administration		
	24	48	72
I	2·5	2·0	1·7
II	3·1	2·1	1·5
III	3·2	1·6	1·2
IV	2·6	2·2	1·9
V	2·4	2·1	1·6

The following experiments were conducted to find out the rate of absorption of sulphapyridine from the peritoneal cavity.

Experiment 1.—Ten control cases were taken. These were all diagnosed as chronic appendicitis, and inflammation was not a factor to be taken into account. Laparotomy by a right paramedian incision was performed, the abdominal cavity explored, and the appendix removed. Before sewing up, 10 g. of sulphapyridine suspended in 4 oz. of saline was placed in the abdominal cavity, and the dregs were lightly rubbed into the wound. Samples of blood were taken at 24, 48, and 72 hours, and 7 days after operation. Readings typical of the results obtained are shown in *Table II*. This table gives the readings obtained in five of the controls, showing the close similarity of the readings, which was true of all the cases. A week after operation the readings varied between 0·4 mg. and 0·7 mg. per 100 c.c.

Experiment 2.—Blood-levels were taken from a series of cases in which inflammation was present and there was free fluid or pus in the peritoneal cavity. This series included cases of appendicitis with free fluid, appendicitis with general peritonitis, pelvic abscess, and perforated gastric ulcer. The dosage

Table III.—Blood Concentration of Sulphapyridine (mg. per 100 c.c.) in Five Cases of Peritoneal Inflammation of Varying Degree after Intraperitoneal Implantation of 10–15 g. of Sulphapyridine in 6 oz. of Saline

Description of Case	Hours after Administration		
	24	48	72
Perforated appendix with general peritonitis. Drainage	3·3	1·7	1·4
Appendicitis: Appendix acutely inflamed at tip. Peritoneum inflamed and raw in appendix bed	5·0	2·6	2·2
Acute appendicitis with free fluid. Drainage	2·7	2·4	1·8
Acute perforated appendicitis with general peritonitis. Death three weeks after operation from a subphrenic abscess and empyema	3·7	2·4	2·0
Pelvic abscess. Bilateral salpingo-oöphorectomy for bilateral tubo-ovarian abscess. Drainage of abscess	1·8	1·5	1·3

in these cases was 10–15 g. suspended in 4–6 oz. saline. Allowance must be made for a slight loss through overflow of the substance during introduction, which it is not always possible to avoid, although about one-half was introduced via the drainage tubes at the end of the operation. The findings are shown in *Table III*.

Comparison of *Tables II* and *III* shows that there is little variation in absorption whether gross inflammation or pus formation is present or not, so that sulphapyridine does not differ in this respect from other drugs of the series. But the rate of absorption shows a much slower and more gradual fall, and zero was not reached even at the end of the week, readings averaging 0·5 mg. per 100 c.c. being consistently obtained whether inflammation was present or not. Large individual variations in the rate of absorption are occasionally found; readings as high as 15–17 mg. per 100 c.c. have been recorded in a case of hemicolectomy for carcinoma of the cæcum and in a case of perforated duodenal ulcer. These, however, are exceptional. Opportunities for direct observation to ascertain whether any of the drug remains after operation are rare. White granules of the drug can be seen coming out of a drainage tube from the abdomen in a few cases several days after administration, but this is not usual, and I have only noted it if gross suppuration was present at operation. One case, however, is worthy of record:—

Case 1.—A woman of 58 was admitted with an advanced carcinoma of the rectum, deemed just to be within the bounds of operability. She was prepared for an abdomino-perineal resection, which was subsequently performed by Mr. C. A. Joll. During the operation the extremely friable growth ruptured and the peritoneal cavity was grossly contaminated with bowel contents; 15 g. of sulphapyridine in saline was placed in the abdomen and a further 15 g. in the perineal wound. She never recovered completely from post-operative shock and developed chest complications from which she died 84 hours after operation. The abdomen was opened post mortem, through the original incision, which showed no obvious sulphapyridine. There was no free fluid or pus in the peritoneal cavity, and the sulphapyridine was in process of absorption. At a very rough guess about 25 per cent of what had been put in remained as small clumps about the size of a pin's head on the small gut and posterior wall. There were no signs of inflammation or adhesion formation.

Ryan, Bauman, and Mulholland (1942) record the blood-levels and urinary excretion of sulphadiazine following its introduction into the peritoneal cavity of six patients. In three of these, receiving 10 g. each, the figures ranged as in *Table IV*.

The peak absorption occurred between 12 and 36 hours after administration, and it will be noted that the figures, although a little higher, are similar to those which I obtained with sulphapyridine. They recorded much higher readings in two other cases using 20–25 g. of the drug. There were no apparent post-operative or toxic complications. Sulphapyridine and sulphadiazine are, therefore, the slowest of the four common sulphonamide drugs to be absorbed from the peritoneal cavity, which is in accordance with their low solubility.

Table IV.—Blood Concentration of Sulphadiazine (mg. per 100 c.c.) in Three Patients after Intraperitoneal Implantation of 10 g. of Drug (*After Ryan, Bauman, and Mulholland*, 1942)

Case	Hours after Administration		
	24	48	72
I	6·0	3·7	2·5
II	5·7	4·5	1·5
III	4·7	1·6	1·1

METHODS OF ADMINISTRATION AND DOSAGE

Sterilization of the sulphonamide powders was not generally thought necessary until the report of a case of tetanus which proved fatal seven days after operation for a suppurative condition in the pelvis of a woman. Sulphapyridine had been sprinkled into the pelvis before the closure of the abdomen. The verdict of the Coroner was death by misadventure from tetanus, due to infection from a sulphapyridine container (*Lancet*, 1942; Atkinson, 1942; Sandes, 1942). Before the report of this case I had placed the powder in the abdominal cavity, from the cardboard containers, in upwards of fifty cases. An effective technique for sterilizing sulphonamide powders has been evolved (Medical Research Council, 1943) and sterile preparations should now be exclusively used.

It is necessary to consider whether there is any other way of administering sulphonamides which is superior to the intraperitoneal route in the treatment of peritoneal infections. Cokkinis (1938) reported favourably on the oral use of sulphonamides in acute appendicitis after operation, whether contaminated or not, and especially in cases of late acute appendicitis with localized lump formation without obvious abscess development; in these the drug seemed to hasten resolution. Favourable results were also obtained in frank peritonitis, and in a case of subphrenic abscess. No actual figures were published.

Corry, Brewer, and Nicol (1939) reported the use of sulphonamides by various routes other than the peritoneal in the treatment of peritonitis of appendicular origin; they summarized 41 cases of appendicitis with varying grades of abscess formation and peritonitis, with apparently favourable results. A series of 273 cases of acute appendicitis with a mortality rate of 1·1 per cent compared favourably with a previous five-year period which showed a mortality rate of 5·3 per cent. Toxic manifestations were frequent in this series, sometimes necessitating stopping administration of the drug.

Rosenberg and Wall (1941), experimenting with artificially produced peritonitis in rats,

showed that the intraperitoneal route was definitely superior to the subcutaneous. Stafford (1942) reported 479 cases of peritonitis or abscess of appendiceal origin at the Johns Hopkins Hospital with a mortality rate of 10 per cent, but since using sulphathiazole in such cases, either by mouth or intravenously, the mortality rate had been reduced 50 per cent. Complications were few and the blood-level was kept at 6–8 mg. per 100 c.c. Hudson and Smith (1942) stated that their results, using any route other than the intraperitoneal, were disappointing. In their inquiry into the best way of controlling infection in abdominal war wounds, Gilchrist and his colleagues (1943) demonstrated in dogs that sulphanilamide by mouth will not produce adequate early concentrations in blood and peritoneal exudate.

From the patient's viewpoint, there have been far more undesirable features in these other routes of introduction, of which vomiting and prostration have been the most unpleasant. They are distressing in the extreme to a patient already ill with an abdominal disease, and seem to be avoidable by using the intraperitoneal route. Intramuscular injection may produce severe pain at the site of injection, and such catastrophes as nerve palsies must not be forgotten. The intravenous route seems to be best if the drug is to be given systemically, and it can be given via a drip saline. If the intraperitoneal and other routes are combined there seems to be a special danger of jaundice (Jackson and Coller, 1942).

Care must be observed in the application of the drugs to the peritoneal cavity. The powder may be (1) dumped in; (2) sprinkled in from a perforated container on the 'pepper-pot' principle; (3) dusted in by means of a sterile gauze swab. These may be termed the dry methods of application. Dumping and sprinkling are, however, inadvisable, for there is a great tendency for too much powder to accumulate at one spot. This, to my mind, is the most fertile cause of subsequent adhesions, particularly with the drugs which have a low rate of absorption. I have frequently noted in my earlier cases that if any large mass of the drug is allowed to fall into the peritoneal cavity in one place it is rapidly enmeshed by the peritoneum, and so firmly that only vigorous wiping will remove it, and this may result in a tearing of the bowel surface. Crutcher and his colleagues (1943) have observed in dogs that sulphonamides introduced in lump become walled off as a foreign body and are absorbed very slowly; they noted that fine powders are more liable to form lumps than coarse crystals. Dusting the powder over the bowel surface with a soft gauze swab is a useful method to employ around an anastomosis of bowel or wherever a definite local concentration of the drug is desired.

Apart from such dusting, the drugs should always be applied in a fluid suspension; a solution is not possible owing to their low solubility. The suspension is best made by rapidly stirring the finely powdered drug in sterile saline. For 10–15 g. of the powder about 6–8 oz. of sterile saline is necessary. The powder is rapidly stirred until a thin watery emulsion is obtained. This is then at once transferred to the peritoneal cavity and is best squirted in rapidly with a 10- or 20-c.c. Record syringe, so that a jet of the emulsion is sprayed over the contents of the peritoneal cavity. The drug will then be seen to adhere to the peritoneum in small clumps over very wide areas and gross dumping of large masses will be avoided. This method makes for easier absorption, and obviates adhesion formation. The one drawback is the spilling of the emulsion over the edges of the wound, so that a quantity of the powder is lost. This is especially the case if the anæsthetic does not give good relaxation. If a spinal anæsthetic has been used, the 'negative' intra-abdominal pressure and laxity of the muscles allows the fluid to be squirted or poured in quite easily and little will escape. If introduction is difficult and drainage is to be used, some of the suspension may be injected down the tube after the complete closure of the abdomen. A spigot must be at once inserted to prevent overflow. Hudson and Smith (1942) recommend the use of an indwelling catheter, led into the cavity through the abdominal wound; the suspension can be injected down the catheter, which is then clipped off. Further quantities of the suspension can be introduced on future occasions if deemed advisable, although they say that these may cause considerable pain.

I have employed the method only once and the patient did not seem to suffer discomfort. The spigot of the drainage tube should be removed six hours after operation to allow normal drainage to begin. The dregs of the emulsion can be rubbed lightly into the separate wound layers. If pus is present, it should be removed, either by gently swabbing, or, if in great quantity, by a sucker, but it is never easy to clear out all the purulent products. It is, however, highly important to do this as far as possible, in order to remove the inhibitors of the drug, of which pus is a fertile source—a point first emphasized by Tashiro et al. (1942).

Chambers et al. (1942) have described the reduction in the size of sulphathiazole crystals by the method of sonic agitation. By this method minute crystals, uniform in size, are produced which will give a stable aqueous suspension with little tendency to settle. The micro-crystals will pass through a syringe needle. A quicker absorption is noted with these small crystals, especially during the first two hours. Clumping is easily avoided, and if such a suspension is placed in the abdominal cavity, it rapidly spreads over the intestinal surface. This type of preparation seems to possess distinct advantages for intraperitoneal use.

Solutions of the soluble forms of sulphonamides are unsuitable for intraperitoneal administration, on account of their very high alkalinity

and consequent strong caustic action. This is especially true of sodium sulphapyridine. Yet Fox (1942) has conducted experiments in mice and dogs in which the sodium salts of sulphapyridine, sulphathiazole, and sulphadiazine were introduced into the muscles and peritoneal cavity. His results showed a rapid absorption with good healing and no obvious necrosis. He suggests, therefore, that clinical trials with these solutions are warranted. Even if further experiment confirms that they are not seriously irritating, they will not supplant powder when it is essential to maintain a high concentration at one place—e.g., along a line of anastomosis. Furthermore, their absorption may be too rapid; the object of a powder is to keep a good concentration in situ for as long as possible.

Investigators have widely divergent views on dosage. Ryan, Bauman, and Mulholland (1942) have given up to 25 g. with no ill effects, whereas Jackson and Coller (1942) advised against doses greater than 5 g. Dosage must depend on the condition found at operation. In the absence of frank pus or gross inflammation small doses suffice, and 10 g. in 4 oz. of saline is adequate. I generally use 15 g. of sulphapyridine in 6 oz. of saline in contaminated cases, remembering that it is impossible to prevent the loss of a certain amount from spilling and overflow. If frank suppuration is present, far higher doses are required, because of the inhibitory powers of pus, and I have inserted 25 g. of sulphapyridine with no toxic results.

COMPLICATIONS

In the cases in which I have used sulphapyridine in the abdominal cavity, the complications which might ensue, and which are often troublesome when the drug is given by mouth or injection have been entirely absent; there has never been any cause for anxiety due to development of a toxic state from the drug. The dose has usually been 15 g., and this amount has been used in the abdominal cavities of children in serious infections. I attribute the lack of toxicity to the slow absorption of sulphapyridine as compared with sulphanilamide, although sulphathiazole has been the cause in some cases. Lyons and Burbank (1942) studied the toxicity of the sulphonamides to living cells, noting the depression of cell development and the limitation of cell growth, and concluded that sulphanilamide is more toxic than other chemotherapeutic drugs, on account of its higher solubility. This was also true of its action in the suppression of the red and white blood-corpuscles, whereas subsequent toxic effects were not observed with sulphapyridine or sulphadiazine.

General Complications.—

Blueness.—One thing which will always strike the surgeon after the introduction of the drugs into the peritoneal cavity is the blue colour of the skin. This appears to have little significance, as the blueness rapidly disappears, although it is often more marked than with oral administration while it lasts. Hudson and Smith (1941 and 1942) remarked on this blue coloration, but they had observed no serious toxic symptoms with sulphanilamide.

Depression and Restlessness.—No patient of mine has complained of the extreme depression commonly encountered after oral administration, and I have seen no published reports of this as a complication of intraperitoneal administration. At times after relatively large doses in young children I have noted extreme restlessness and what appears to be disorientation comparable to that seen after oral administration; but these children have all been suffering from a severe illness, and it is difficult to know to which cause one should attribute such signs.

Vomiting.—Beyond that which can readily be attributed to a post-anæsthetic complication, vomiting never occurs with intraperitoneal sulphapyridine, and I have not seen it reported with the other drugs used. This is extremely important, and, as Pearl and Rickles (1942) pointed out, oral administration is not desirable and is often impossible in a patient very ill with an abdominal complaint because of vomiting.

Jaundice.—Reports from America stress the possible occurrence of severe jaundice. Sulphanilamide placed in the peritoneal cavity is probably absorbed by the portal system and carried to the liver in high concentration; this may account for the jaundice, which is not seen if the drugs are used in peripheral wounds, where it will be absorbed into the caval system (Lyons and Burbank, 1942). Jackson and Coller (1942), experimenting with dogs, showed that if sulphanilamide was used intraperitoneally there was always a higher concentration of the drug in the portal blood than in the systemic. They also recorded a number of cases in which definite jaundice developed—9 out of 29 patients so treated—if the sulphanilamide was administered by other routes as well as the intraperitoneal, and the jaundice was due to hepatic damage. The jaundice seemed to clear without permanent results, but because of it they advise only modest intraperitoneal doses. Watson and Spink (1940) believe that a mild liver damage, secondary to toxic drainage from intraperitoneal sepsis via the portal vein, can be converted into outspoken hepatic dysfunction and jaundice if the toxic effects of the sulphonamide drugs are superadded.

Bieter et al. (1941) show in children that with sulphanilamide, even if given orally, there is a selective concentration in the liver, as compared with sulphapyridine and sulphathiazole. Davis (1942) also points out that sulphanilamide should not be used if there is any suspicion of liver damage, as it may make the damage considerably worse, and also states that 6 g. is the highest safe intraperitoneal dose if such a complication is to be avoided. Hudson and Smith reported no cases of jaundice with sulphanilamide or sulphathiazole, and I have never encountered a case

with sulphapyridine even from massive doses in severely toxic patients.

Agranulocytosis.—This must be a very rare complication of intraperitoneal chemotherapy, if it ever occurs. I have never seen it in my own cases, and I have only read of one possible case elsewhere (Lesses and Starr, 1942).

Renal Complications.—There has not yet, as far as I know, been any case of anuria recorded as a complication of intraperitoneal chemotherapy, but since several fatal cases of anuria, and some successfully treated, have followed the use of sulphapyridine by mouth, some mention must be made of it here.

Case 2.—I recently operated on a child for appendix abscess (which would have been better treated on expectant lines), and as free pus was liberated I followed my usual routine and placed 10 g. of sulphapyridine into the peritoneal cavity. The child's urine was passed normally for three days after operation, but he passed only 1 oz. from 9 a.m. on the third day until 2 a.m. next morning, when he passed 12 oz. From 2 a.m. until 8.15 p.m. on this fourth day he passed no urine, but at the end of that time he passed 10 oz. It was scanty on the fifth day, and he passed 8 oz. on the evening of the sixth day. This gave cause for anxiety, but from the seventh day his urine output rapidly became normal and a clean specimen examined showed only occasional red blood-corpuscles.

I have also seen hæmaturia result from the prolonged application of sulphapyridine to large raw areas following burns in children. It is therefore important to watch for this serious complication, carefully to control the dosage in a child, and to see that adequate fluids are given by mouth in all cases, supplemented by rectal administration in children if necessary (a far better method in children than via the veins).

Local Complications.—

Inflammation, Adhesions, and Non-absorption.—When any substance is injected into the peritoneal cavity a reaction occurs which results in peritonitis, variable in degree. The nature, amount, and type of substance introduced will naturally determine the type and severity of the reaction (Harvey, Meleney, and Rennie, 1942). Any chemotherapeutic drug will thus cause a reaction in the peritoneum; but if the reaction helps to marshal the body's defences against a serious infection it will assist in overcoming such infection. If, however, it is too severe or too prolonged, adhesions may be left behind.

The possibility of the formation of adhesions has received a great deal of attention in the literature, ranging from a deprecation of the use of sulphonamides in the peritoneal cavity altogether on account of the danger of such adhesions and other evils (Taylor, 1942), through a warning that adhesions may occur, to a frank denial that adhesion formation is of much importance. Jackson and Coller (1942) found that there was little reaction on the part of the peritoneum in dogs when sulphanilamide was introduced, as evidenced by hyperæmia or adhesion formation, and also believe that scarring may actually be prevented by its introduction. Autopsies on two of their patients who had been treated by such methods showed little peritoneal reaction with very few adhesions. Laird and Stavern (1942) examined the peritoneal reaction in dogs, using sulphanilamide and sulphathiazole. They found that these drugs produced no reaction or adhesions and there was no trace of the drug four weeks after introduction. The sodium salt of sulphathiazole, however, produced pronounced adhesion formation and inflammation, due to its high alkalinity (*p*H about 10). The alkalinity of the soluble form of these drugs definitely precludes their use in the peritoneal cavity, and the only sodium salt which can be used in solution is sulphacetamide soluble, which is neutral, but a solution has no advantages over a powder.

Laufman and Wilson (1942) showed that sulphanilamide was relatively non-irritant to the peritoneum of rats, and this has been confirmed in the same animal by Throckmorton (1941), using both sulphanilamide and sulphathiazole. He further reported that sulphapyridine had a marked irritant action, leaving many adhesions and large quantities of the drug walled off. Hawking and Hunt (1942) reported that sulphadiazine placed in the peritoneum of dogs remained cut off and walled off by adhesions. Walter and Cole (1943) observed some adhesions in dogs after the intraperitoneal insertion of sulphadiazine, but these were never dense; there were no adhesions after sulphanilamide. Crutcher and his colleagues (1943) found that sulphanilamide, sulphathiazole, and sulphadiazine may all produce adhesions if they are not well spread about; sulphanilamide was least liable and sulphadiazine most liable to produce adhesions. Sutton (1942) reports the case of a boy who was operated on for acute gangrenous appendicitis and peritonitis and in whom the intraperitoneal use of sulphathiazole was followed by adhesions and intestinal obstruction, necessitating a second operation about three months afterwards, when dense adhesions were found in the right iliac fossa. The cause of the obstruction—the crystals of sulphathiazole—had disappeared. He also stated that there was delayed wound healing and a keloid scar. Only 3 g. was sprinkled into the peritoneal cavity and the area was drained.

There has been no reference to the reactions produced by sulphapyridine except that Throckmorton has stated that it was highly irritant to the rat peritoneum, producing well-marked adhesions, and that particles of the drug were left behind. Though I have nearly always used the drug in my own cases I have encountered adhesion formation in two cases only (reported below), and in neither could the use of the sulphapyridine be blamed as the cause. The following case suggests that sulphapyridine does not tend to produce adhesions or to remain in situ for an undue time.

Case 3.—A woman aged 41, was operated on in 1941 for acute appendicitis and early peritonitis (Gardiner, 1942). She made an uninterrupted

recovery except for a slight left basal pneumonia. The peritoneal cavity was drained through the lower end of the incision, which was a right paramedian. She was re-admitted one year later complaining of a slight hernia through the lower end of the scar where the drainage tube had been inserted. An operation for repair was performed, the old scar excised, the wound layers defined by dissection, and the peritoneal cavity opened. There were no signs of the sulphapyridine, or of any adhesions except some purely local ones around the great omentum and the back of the abdominal scar, and a very few filmy ones in the right inguinal fossa, round the cæcum. These were separated with great ease and a repair carried out.

In *Case* 1, the abdomino-perineal resection for advanced carcinoma of the rectum in which the growth ruptured, the sulphapyridine four days after operation was in the process of absorption and only minute clumps remained.

I have recently been able to confirm the absence of gross adhesion formation in further cases following the use of sulphapyridine in peritonitis. One case, an old man of 75, who was operated on for advanced general peritonitis, following a ruptured appendix, died three weeks after. He developed paralytic ileus five days after the operation, from which he never recovered in spite of treatment. There were but few adhesions found post mortem. His abdominal wound (a right paramedian incision) healed firmly.

The following two cases were complicated by adhesion formation following operation :—

Case 4.—H. M., aged 7 years, was admitted to hospital on Nov. 29, 1943, with a history of 24 hours' abdominal pain and vomiting. Pulse 116; respiration 24; temperature 103°. Chest and urinary system normal. He had marked generalized abdominal pain and tenderness. A diagnosis of appendicitis with peritonitis was made and operation was performed the same evening. Through a right paramedian incision a high cæcum was mobilized with difficulty, due to gross inflammation and free pus. A gangrenous retrocæcal appendix was removed with difficulty. Sulphapyridine (15 g.) was instilled into the abdominal cavity and the wound powdered. The abdomen was drained. His progress for the first five post-operative days was good, and his bowels were well opened with enemata on the third and fourth days. After this, however, he was not so well, and on the seventh day he began to show signs of obstruction, with onset of distension. He began to vomit on the eighth day and on the ninth radiography revealed distended coils of gut with fluid levels, with obstruction probably at the ileocæcal valve. His abdomen was opened through the original incision and the terminal coils of ileum were found bound together with loose adhesions. Inflammation was gross. The adhesions were separated easily and the obstruction relieved. Three clumps of sulphapyridine the size of large beads were found adhering to the bowel wall firmly; the rest was practically absorbed. They were not removed. The abdomen was closed and the child made an uninterrupted recovery except for a breakdown of the superficial layers of the abdominal wound which took some time to heal up.

Case 5.—J. McC., aged 51 years, was admitted to hospital on June 2, 1943, with a history that he had been suffering from abdominal pain and upset for one week. This had begun previously as a severe central abdominal pain which subsided but had come on again with extreme violence and he had been vomiting. On examination he was an extremely sick-looking man with a hard, blown-out, distended abdomen. His temperature and pulse were normal. As it was a definite case of an abdominal catastrophe, operation was performed the same night and he was found to be suffering from very advanced general peritonitis due to a perforated inflamed Meckel's diverticulum. The whole of the abdomen was full of small-gut contents with severe inflammation and pus formation. The diverticulum was removed and the abdomen drained by two large tubes. Sulphapyridine (25 g.) was injected into the abdominal cavity. Following this operation he appeared to make a good recovery and for the first ten days following the operation went on very well, his appetite, bowel actions, etc., returning. About the tenth post-operative day, however, he began to show signs of an obstruction and in the ensuing eight hours this became much more marked and was confirmed by radiographs, which showed fluid levels. His abdomen became distended and he began to vomit violently. He was seen by Mr. C. A. Joll in consultation, who advised an immediate further laparotomy, which was performed on June 16. On opening the abdominal cavity, practically the whole of the small intestine was found matted up together with a vast number of thin filmy adhesions, and there was a high obstruction. Efforts were made to free these adhesions without success. Residual amounts of the sulphapyridine were found lying between the coils of gut and also in the pelvis. He did not recover from this operation, but died on June 18.

The type of adhesions which were seen in this case were exactly similar to those which I have found in cases of strangulated hernia which have been described by other writers and they are, in my opinion, almost exclusively confined to cases in which the peritoneal cavity has been grossly contaminated with small-gut contents. I do not think it is true to say that the contents of the small gut do not cause gross peritoneal inflammation or subsequent adhesion formation, as it has always been in these cases that I have found a widespread plastic peritoneal reaction, and I think, further, that the peritoneum of some individuals is more prone to irritation by small-gut contents than are others. I do not think that the sulphapyridine in these cases was the cause of the adhesions.

It appears that slight adhesion formation will occur whatever the drug used, and in certain individuals who have a natural tendency to form adhesions. All surgeons know that, after operations for inflammatory and other abdominal conditions, dense adhesions do form in a few cases, and this will happen whatever form of intraperitoneal chemotherapy is employed. The risk is undoubtedly outweighed by the advantages to be gained from these drugs; it will not be great if, as far as possible, an even distribution is obtained, and the dumping of a mass of powder in any one area is avoided.

Delayed Healing.—There has been much controversy on this aspect of chemotherapy. Bick (1942) concluded that the local application of sulphonamides to wounds of soft tissue at a clean operation, in which primary suture was indicated, reduced the rate of healing by 5 per cent, and also caused extensive cutaneous scarring. The scars also seemed to be greater in depth and breadth. Taylor (1942) placed sulphathiazole, sulphanilamide, and sulphadiazine beneath the rectus sheath in dogs, and found that sulphathiazole and sulphadiazine caused actual abscess formation, and there was inflammation with sulphanilamide. Apart from these two papers and the isolated case of Sutton (1942) already mentioned, most reports speak well of the effect of the drugs on wound healing and in the prevention of suppuration and subsequent breaking down of the wound. Key and Burford (1941) report from animal experiment that there is no interference with the healing of the soft tissues if sulphanilamide is implanted, provided certain precautions are observed. They now implant the powder as a routine in all wounds. The powder should be lightly sprinkled in the wound and too much should be avoided, as this tends to cause serum outpouring. They found that by using the powder as a routine, the incidence of stitch abscess was less and that all wounds, in a series of 150 cases, healed by first intention. Davis (1942) and Mueller and Thompson (1942) state that sulphonamides stimulate healing.

In a previous communication (1942) I drew attention to the excellent healing obtained in contaminated wounds following laparotomy for peritonitis or a ' dirty ' appendix if sulphapyridine was employed. Similar cases have further convinced me of the efficacy of the drug in preventing breakdown and suppuration of the wound, with their attendant evils, such as prolonged stay in hospital while the wound granulates, burst abdomen, wound phagedæna, and subsequent herniation through the scar. In the past eighteen months I have ceased to drain any contaminated wound, but have gently rubbed a fine emulsion of powdered sulphapyridine in saline into the wound layers, prior to closure by primary suture. In not one of the cases, although often freely contaminated, has a breakdown occurred. Most of them healed by first intention, and in a few a little purulent fluid escaped which subsequently dried up with sound wound healing. Nor does there seem to be any acceleration in the absorption of the catgut (Adeney, 1941). Drainage tubes have often been employed in cases of gross contamination of the peritoneal cavity, but the hole for the tube alone has remained open for drainage of the pus, the rest of the wound healing soundly. In one case an incisional hernia occurred, but this was through a drainage tube hole, used to drain the pelvis in pelvic appendicitis. It should not be necessary to apply the sulphonamide in a surgically clean wound, but if used properly in such cases it should do no harm. I have not observed any excessive keloid formation after the use of the drugs.

RESULTS IN ACUTE ABDOMINAL CONDITIONS

1. Appendicitis.—The largest number of reports of intraperitoneal chemotherapy have the treatment of acute appendicitis and its complications as their basis. In the short time in which it has been in use this procedure has done much to lower the mortality in complicated appendicitis. Thus, Hudson and Smith (1942) showed a fall in mortality in cases of peritonitis and peritoneal contamination from 18·4 to 6·4 per cent. From 1935 to 1939, 741 cases of acute suppurative appendicitis were treated at the Roosevelt Hospital in New York with 20 deaths, a mortality rate of 2·7 per cent; in 1940, 204 such cases were operated on, but these also received intraperitoneal sulphanilamide therapy and there were no deaths. Thompson, Brabson, and Walker (1941) reported its use in 59 cases of acute diffuse appendicitis with favourable results, some of the cases appearing to be hopeless. Anderson (1942) reported 22 cases of advanced acute appendicitis treated by operation and intraperitoneal sulphathiazole (5 cases also received additional sulphathiazole either intravenously or orally) with one death, a mortality rate of 4·5 per cent. Pearl and Rickles (1942) produced a pure *B. coli* peritonitis in rats and found that sulphathiazole afforded complete protection if the drug was given at the time of introduction of the bacteria; in diffuse peritonitis one rat died, whereas all the control cases ended fatally. Epps, Ley, and Howard (1942) experimented with dogs in which a perforating appendicitis was produced, and sulphanilamide, sulphapyridine, and sulphathiazole were placed in the peritoneal cavity at intervals in the course of the illness; sulphathiazole gave the lowest mortality rate.

I have used sulphapyridine in all stages of acute appendicitis over the past two and a half years and the results have been gratifying. Seemingly hopeless cases of general peritonitis have made a rapid recovery, and many less advanced cases have done extremely well. Exudate was either reduced to a thin serous yellow discharge which did not last long, or if purulent did not continue for anything like the time it did before I used sulphapyridine. There have been three deaths, two reported above, and another in an advanced case of general peritonitis in which the whole abdomen was full of pus, and a pelvic abscess developed which cleared satisfactorily, but a right posterior subphrenic abscess formed subsequently, and I unfortunately delayed drainage too long. I still feel that drainage should be instituted in all cases where there is any doubt in the surgeon's mind. Nothing is to be lost by drainage, and, if frankly purulent discharge does not develop, the tube can be removed within 24–48 hours. It must not be assumed from the published results that a purulent discharge will

never occur; but if drainage has been employed the surgeon can feel safe. Wound healing has been remarkable in cases receiving intraperitoneal sulphapyridine in the presence of the grossest contamination; whatever the type of incision, healing by first intention has nearly always occurred. One or two obese patients have had superficial abscesses which have drained for a few days, but there has never been a major breakdown of the wound and the final healing has been gratifying. In grossly contaminated cases which have been drained by a large tube let into the pelvis, healing has been just as sound and a clean granulating hole left when the tube has been withdrawn. I never drain the individual wound layers as in the past. This means that both immediate complications, such as wound phagedæna, and remote ones, such as ventral hernia, should become increasingly rare.

Finally, the time spent in hospital is immensely reduced, some cases of general peritonitis leaving after ten days only. In the past it has not been unusual for such a case to remain in for weeks, with a persistent purulent discharge.

It must not be assumed that chemotherapy is the complete panacea for peritonitis after appendicitis. Two facts interfere with the results—a mixed infection, and the presence of much free pus, usually due to a widespread peritonitis of some days' duration. If a pure culture is obtained at operation, for example *B. coli* alone, the results of treatment are good; but if a mixed culture is obtained, for example, *B. coli* and *Str. fæcalis*, healing is much slower. A large quantity of pus inhibits the action of the drugs, and in such cases the method loses a good deal of its efficacy. Possibly some chemotherapeutic compound will be discovered which will not be so inhibited, or the drug will be combined with an efficient neutralizer of those inhibitors. At present we can only use the drug in increased doses in such cases and clear the cavity of as much pus as possible at operation.

2. Perforated Peptic Ulcer.—I have employed chemotherapy in only two cases of perforated peptic ulcer, and of these one had been perforated for 28 hours and the other for 22 hours before operation. The first patient died the day after operation, but the second made an excellent recovery. My other cases have all been operated on within 12 hours of perforation, and I did not employ chemotherapy because these early cases do well without. Griswold and Antoncic (1941) treated 111 cases of perforated peptic ulcer with intraperitoneal sulphanilamide, with 20 deaths. Wakeley (1944) advocates its use in these cases.

3. Perforated Diverticulitis.—In my series there have been three cases, two previously reported (Gardiner, 1942), and a third in which, in addition to the use of chemotherapy, I exteriorized the loop of the sigmoid colon involved, owing to the extent of the perforation, and the patient died. The two other cases were successful, and no colostomy was performed in either.

4. Intestinal Obstruction.—Hudson, Smith, and Selbie (1941) give figures of the high mortality rate still found in acute intestinal obstruction. The two commonest causes of obstruction were strangulated hernia and carcinoma of the colon. They pointed out that the cause of the high mortality rate, especially in small-gut obstruction, was late diagnosis with a consequent late institution of treatment, and that the prognosis was bad if resection of bowel had to be performed instead of simple release. Where simple release alone was practised, the mortality rate was 5·2 per cent, but if a resection was required, it was 77·4 per cent. This very high fatality rate in cases requiring resection was ascribed to peritonitis developing owing to the escape of the gut contents and contamination at the actual operation. Experiments with rabbits showed that intraperitoneal sulphanilamide prevented the development of peritonitis when the cavity had been contaminated with the cæcal contents, and that it reduced the inflammation following resection of the gut. There is little doubt that the mortality rate would be much reduced if the risk of the plastic peritonitis found in these cases some days or weeks after operation could be abolished. They reported three cases of strangulated hernia requiring resection of gangrenous gut, with subsequent recovery (loc. cit., Hudson and Smith, 1942), and I have had two such cases. Of my two, one, previously reported, died, but the other recovered from operation.

Case 6.—An elderly man operated on for a strangulated right femoral hernia. The gut was found to be non-viable; about 1½ ft. was resected and an end-to-end anastomosis performed. The line of anastomosis was carefully powdered with sulphapyridine, the gut replaced in the abdominal cavity, a catheter fed into the cavity through the dilated neck of the hernial sac, and 20 g. of powdered sulphapyridine in saline squirted in. A Lothieson type of repair was then performed, the whole operation being completed from below. In spite of his poor general condition (he was recovering from influenza and bronchitis), the man made an uninterrupted recovery.

It is to be hoped that surgeons will try out similar treatment with other cases.

5. Pelvic Abscess.—I have treated two acute cases of this condition, the cause in both being pyosalpinx and tubo-ovarian abscess. A radical operation was carried out in both, all the diseased tissue being removed and the pelvis drained. Both made an excellent recovery, with far less discharge than is usual, and sound healing. The third case, operated on by Mr. V. J. F. Lack, was a chronic suppurative condition of the pelvis, due to bilateral tubo-ovarian abscesses. Twice before the patient had had simple drainage of a pelvic abscess performed. All the diseased tissue was removed, the pelvis was filled with an emulsion of 15 g. of sulphapyridine in saline, and the pelvis drained. The wound was liberally treated with sulphapyridine powder. She drained for approximately three weeks, but the wound, a left

paramedian incision, healed soundly by first intention, whereas after the two previous operations she was left with a large right ventral hernia.

6. Miscellaneous.—I have used sulphapyridine in isolated cases of other acute abdominal emergencies and operations resulting in contamination—for example, empyema of the gall-bladder, drainage of the common bile-ducts, intussusception, internal obstruction of the small gut due to adhesions and in one case to a phytobezoar necessitating opening of the ileum for its removal (Gardiner, 1943), all with good results. It is evident, therefore, that there is a wide scope for intraperitoneal chemotherapy in the surgery of the acute abdomen, both as a prophylactic and curative measure. Brief reports of typical cases with the results obtained, etc., are presented in *Table V*.

PRIMARY PERITONITIS

I have had only two cases of primary peritonitis, both due to the pneumococcus :—

Case 7.—A girl aged 8 years, admitted with a history of 6 days' illness, ushered in with diarrhœa and vomiting, followed by abdominal pain. She was extremely toxic and ill on admission, temperature 102° F., pulse 116, with a tender distended abdomen, generalized guarding, and pain and tenderness in the right inguinal fossa. A diagnosis of general peritonitis from a perforated appendix was made. She was operated on at once and a gridiron incision was used, but on opening the abdomen thick greenish-yellow pus poured out, a good deal of it in the form of flakes. There was generalized inflammation of the whole of the peritoneal contents, but the appendix, apart from the general reddening, was normal. A primary pneumococcal peritonitis was diagnosed and culture later showed pneumococcus, Type I. The appendix was removed, a suprapubic stab drain inserted, and a fine soft rubber catheter placed in the abdominal cavity and brought out of the gridiron incision before closure; 15 g. of sulphapyridine in saline was instilled into the cavity at the end of the operation. Subsequent blood examination showed a sulphapyridine level within the usual limits. The course of the illness after operation was not satisfactory. On the fifth day the suprapubic tube was removed and the catheter slowly withdrawn. Thick greenish-yellow pus continued to be discharged, and the temperature remained at 100°–101° F. during the first ten days, rising to 103° F. on the eleventh day, when a further 5 g. of sulphapyridine in saline was instilled into the abdominal cavity via the catheter. This caused no pain or discomfort. The dose was repeated on the fourteenth day, but there was no change in the temperature or in the amount of discharge. A course of sulphapyridine by mouth was started on the eighteenth day and a slight drop in temperature was noted, but a blood-count revealed a total leucocyte-count of 2000 per c.mm. only, with 6 per cent polymorphs, and the drug was at once discontinued. The red-cell count was 3,400,000 per c.mm. The chest then came under suspicion. There was some dullness at the left base, and a radiograph revealed a small effusion at the left base, with some collapse of the left lower lobe. The fluid aspirated from the chest was sterile. The midline stab drain still continued to exude a small amount of yellow pus, but there were no signs of a residual abscess intraperitoneally or in the pelvis. The child's general condition was now good, with fair appetite. The temperature finally settled, and the flow of pus from the abdominal cavity gradually dried up, and she was discharged cured.

In this case I cannot claim that the intraperitoneal sulphapyridine had any dramatic effect. Possibly the fact that the child had been ill for six days and that there was so much pus nullified its full effect.

Case 8.—A girl, aged 5 years, was admitted to hospital on April 12, 1943, with a history of four days' abdominal pain, vomiting of black fluid, and profuse green stools. On examination, she was a pale, poorly nourished, very sick child, with dry furred tongue, dirty mouth, and somewhat tumid abdomen. Temperature 102·6°, pulse 130. There were no other physical signs. A tentative diagnosis of enteric fever or dysentery was made. The following investigations were made :—

Blood : W.B.C. 9000 (79 per cent polymorphs).
Hæmoglobin (Haldane) 84 per cent = 11·5 g. per cent
Stools : No abnormal organisms detected on three occasions.
Urine : N.A.D.
Blood-agglutination tests : All negative.
Blood-culture : Negative.

A course of sulphaguanidine was at once given, and by April 18 the temperature had settled and the pulse fallen, but both rose again on April 22 when the course was completed. On April 28 abdominal paracentesis was done, and a turbulent fluid obtained, which, on culture, gave a pure growth of pneumococcus Type 1, thus giving the diagnosis. Following this a course of sulphamethazine was given, but it had little effect as the temperature and pulse still remained elevated and it was discontinued on May 6. A further course was started on May 11 and, following this second course, the temperature gradually settled and did not rise after May 18. The child was discharged cured to a convalescent home.

Points of importance in this case : (1) Difficulty of diagnosing cases of primary pneumococcal peritonitis; (2) Value of abdominal paracentesis and bacteriological examination from fluid obtained; (3) The disease seems to 'run its course' in spite of the sulphonamide drugs—in this case sulphamethazine was given a trial, but it did not seem to shorten the course of the illness.

It would appear from the published reports that in both the pneumococcal and the streptococcal types of primary peritonitis it is better to treat on expectant lines rather than to operate, provided the diagnosis is not in question. Aspiration of the peritoneal fluid and its microscopical examination will throw light on the diagnosis, and an emulsion of sulphapyridine could be injected into the peritoneal cavity by a needle and syringe. If the diagnosis is confirmed, parenteral or other means of administration, possibly combined with introduction into the peritoneal cavity, will be the best method of treatment in such cases, reserving operation for the opening of residual abscesses, should any form.

CHEMOTHERAPY IN LARGE-BOWEL SURGERY

It has been pointed out that intraperitoneal chemotherapy is far more successful in mild or moderate contaminations which might lead to

Table V.—Details of Results of Chemotherapy with Sulphonamides in Acute Abdominal Conditions

Case	Age and Sex	Disease	Operation	Drug Used in 3–6 oz. Saline	Result	Wound Healing	Length of Stay in Hospital
1	36, M.	Acute retrocæcal appendicitis with free pus	Appendicectomy by gridiron incision	5 g. sulphapyridine	Uninterrupted recovery	First intention	8 days
2	16, M.	Appendicitis—two days' duration	Very inflamed appendix removed via gridiron incision. Free fluid present. Drainage	10 g. sulphapyridine	Uninterrupted recovery	First intention	12 days
3	44, F.	Appendicitis—three days' duration	Appendicectomy retrocæcal, tip inflamed. Free fluid	10 g. sulphapyridine	Uninterrupted recovery except for post-operative bronchitis	First intention	13 days
4	4, F.	Appendicitis—twelve hours' duration	Appendicectomy by paramedian incision	5 g. sulphapyridine	Uninterrupted recovery	First intention	12 days
5	46, M.	Acute on chronic appendicitis. Acute for twenty-four hours	Appendicectomy—right paramedian incision. Very inflamed necrotic appendix removed. Drainage	10 g. sulphapyridine	Uninterrupted recovery	First intention	11 days
6	8, F.	Acute appendicitis with peritonitis—few hours' duration	Appendicectomy—right paramedian incision. Perforated pelvic appendix removed. Two drains inserted	10 g. sulphapyridine	Uninterrupted recovery	First intention	20 days
7	68, F.	Abdominal pain twenty-four hours' duration. Acute appendicitis	Right lower paramedian incision. Very inflamed and swollen appendix, with inflamed coils of gut. Appendix removed. Drainage	10 g. sulphapyridine	Uninterrupted recovery	First intention	17 days
8	49, F.	Abdominal pain thirty hours. Appendicitis	Right lower paramedian incision. Gangrenous appendix removed. Large quantity free pus in peritoneal cavity. Drained by stab wound in right iliac fossa	15 g. sulphapyridine	Uninterrupted recovery	First intention	22 days; retained 8 extra days due to poor home conditions
9	17, M.	Three weeks' history, abdominal pain, diarrhœa, and vomiting varying in intensity. Diagnosed as appendicitis	Gridiron incision. Very inflamed appendix removed. Free fluid	15 g. sulphapyridine	Uninterrupted recovery	First intention	14 days
10	7, M.	Acute on chronic appendicitis	Right paramedian incision. Inflamed appendix. Meckel's diverticulum removed	5 g. sulphapyridine	Uninterrupted recovery	First intention	15 days
11	44, F.	Appendicitis with peritonitis	Right paramedian incision. Appendix removed. Two drains	10 g. sulphapyridine	Uninterrupted recovery, except for slight post-operative chest	Uninterrupted, except for small incisional hernia at lower end of paramedian incision due to drainage tube	15 days
12	70, M.	Strangulated right femoral hernia of (?) several hours' duration. Also acute bronchitis	Hernia freed. 1½ ft. gangrenous gut resected. End-to-end anastomosis	20 g. sulphapyridine	Uninterrupted recovery	First intention	17 days
13	4, M.	Acute appendicitis, with general peritonitis	Right paramedian incision. Appendix removed. Two drains in peritoneal cavity	20 g. sulphapyridine	Uninterrupted recovery	First intention	13 days
14	37, F.	Six months pregnant. Sent in as ? intestinal obstruction	Right paramedian incision. Large quantity free pus in peritoneal cavity. Volvulus of cæcum,	15 g. sulphapyridine	Uninterrupted recovery	First intention	16 days

		eral peritonitis	pendix removed. Two drains in peritoneal cavity				13 days
14	37, F.	Six months pregnant. Sent in as ? intestinal obstruction	Right paramedian incision. Large quantity free pus in peritoneal cavity. Volvulus of cæcum, ascending colon, and half transverse colon found. Right hemicolectomy performed	15 g. sulphapyridine	Uninterrupted recovery	First intention	16 days
15	20, F.	Admitted as primipara in labour. Thirty-six hours after delivery, sudden onset of acute appendicitis with peritonitis	Operation by gridiron incision. Retrocæcal appendix, perforated, removed. General peritonitis, with large amount of free pus. Drainage	15 g. sulphapyridine	Uninterrupted recovery	First intention	14 days
16	15, F.	Very acute appendix	Right paramedian incision. Slight amount free fluid in peritoneal cavity. Appendix removed	10 g. sulphapyridine	Uninterrupted recovery	First intention	11 days
17	4½, M.	Several attacks abdominal pain and vomiting	Right paramedian incision. Retrocæcal appendix abscess found and drained. Large amount of pus	10 g. sulphapyridine	Uninterrupted recovery, except for anuria ? due to sulphapyridine which cured itself. Appendix subsequently removed six months after. Practically no adhesions found	First intention	16 days
18	39, M.	Two days' abdominal pain. Diagnosis—appendicitis	Gridiron incision. Gangrenous retrocæcal appendix removed. Free pus present. Drainage	10 g. sulphapyridine	Uninterrupted recovery	First intention	17 days
19	75, F.	Admitted as acute appendicitis with early peritonitis	Right paramedian incision. Gangrenous appendix, with early general peritonitis. Appendix removed. Drained by stab wound in right iliac fossa	10 g. sulphapyridine	Uninterrupted recovery	First intention	Up 16 days after operation, but retained for further 10 days due to home conditions
20	60, M.	Acute on chronic obstruction due to carcinoma of hepatic flexure	*First operation*: Ileotransverse colostomy performed. *Second operation*: Fourteen days later, right hemicolectomy; leakage of large bowel contents at this operation. Drainage	10 g. sulphapyridine	Uninterrupted recovery	First intention	Discharged 23 days after second operation
21	46, F.	Acute appendicitis, with early peritonitis	Right paramedian incision. Gangrenous appendix with free pus removed. Drainage by stab wound in right flank	10 g. sulphapyridine	Uninterrupted recovery	First intention	14 days
22	43, F.	Appendicitis—eight hours duration	Right paramedian incision. Inflamed, perforated appendix removed. Drainage.	10 g. sulphapyridine	Uninterrupted recovery	First intention	10 days
23	18, F.	One weeks' history abdominal pain, vomiting, and diarrhœa. Diagnosis ? typhoid made outside hospital. Patient very ill—diagnosed as general peritonitis	Right paramedian incision. Huge quantity of free pus evacuated. General peritonitis. Perforated appendix removed. As much pus evacuated as possible. Drainage by stab wound in flank and lower end of incision	25 g. sulphapyridine	Stormy convalescence, but eventual good recovery except for long drainage over many weeks	Slight infection of midline wound, but ultimately healed firmly	Several weeks
24	29, M.	Three-day history abdominal pain and vomiting. Appendicitis	Right paramedian incision. Acutely inflamed appendix removed with free pus. Stab drain in flank	10 g. sulphapyridine	Uninterrupted recovery	First intention	14 days
25	22, F.	Forty-eight hours' abdominal pain and vomiting. Diagnosed as appendicitis and peritonitis	Right lower paramedian incision. Pus and free fluid present. Difficult pelvic appendix removed. Stab drain in right flank	20 g. sulphanilamide	Uninterrupted recovery	First intention	26 days
26	22, F.	Twenty-six hours' history abdominal pain and vomiting. Acute appendicitis	Gridiron incision. Free fluid present. Very inflamed appendix removed. No drainage	5 g. sulphanilamide	Uninterrupted recovery	First intention	12 days

[*Continued on next page*

Table V.—DETAILS OF RESULTS OF CHEMOTHERPHY WITH SULPHONAMIDES IN ACUTE ABDOMINAL CONDITIONS, *continued*

CASE	AGE AND SEX	DISEASE	OPERATION	DRUG USED IN 3–5 OZ. SALINE	RESULT	WOUND HEALING	LENGTH OF STAY IN HOSPITAL
27	76, F.	Five days' history strangulated femoral hernia	Under local anæsthetic. Strangulation revealed; 1 ft. gangrenous gut removed. End-to-end anastomosis	25 g. sulphapyridine and sulphathiazole mixture	Stormy period following operation and death six days after. Post mortem, no peritonitis or evidence of sulphonamides left. Anastomosis intact. Death due to heart failure and bilateral pneumonia	—	—
28	54, M.	Extensive carcinoma of stomach, with pyloric obstruction. Impossible to clear stomach by washouts	Partial gastrectomy. Foul smelling contents poured into peritoneal cavity at operation	20 g. sulphanilamide	Stormy convalescence, but subsequent recovery	First intention	25 days
29	17, F.	Three days' abdominal pain. Acute appendicitis	Right paramedian incision. Slightly inflamed appendix and Meckel's diverticulum removed. No drainage	10 g. sulphapyridine	Uninterrupted recovery	First intention	16 days
30	32, M.	Seven days' history abdominal pain, vomiting, etc. Diagnosed as appendicitis	Right paramedian incision. Some free fluid. Appendix removed. Stab drainage	10 g. sulphanilamide	Uninterrupted recovery	First intention	26 days
31	6½, F.	Thirty hours' abdominal pain, vomiting, etc. Signs of general peritonitis	Right paramedian incision. Cavity full of free pus. Perforated appendix removed. Stab drain in flank	20 g. sulphapyridine	Uninterrupted recovery	First intention	17 days
32	7, M.	Two days' history abdominal pain	Right paramedian incision. Perforated appendix removed. Free pus in peritoneal cavity. Drainage right flank	15 g. sulphapyridine	Slow convalescence. Eventual uninterrupted recovery	First intention	22 days
33	15, M.	Two days' history abdominal pain and sickness. Diagnosis—appendicitis	Right paramedian incision. Free pus on opening abdomen. Perforated appendix removed. Stab drain right flank, also drain through lower end of abdominal wound	15 g. sulphanilamide	Stormy convalescence. Signs of pelvic abscess formation sixteen days after operation. Pelvic abscess drained seventeenth day via rectum	First intention	3 weeks after second operation
34	32, F.	History of two days' abdominal pain and vomiting. Diagnosis of appendicitis	Appendix removed through grid-iron incision. Very inflamed	10 g. sulphanilamide	Uninterrupted recovery	First intention	12 days
35	11, F.	Fifty hours' history of abdominal pain and vomiting. Diagnosed as appendicitis	Right lower paramedian incision. Very inflamed appendix removed with free pus. Stab drain inserted	10 g. sulphanilamide	Uninterrupted recovery	First intention	16 days
36	11, M.	Twenty-four hours' history of abdominal pain and vomiting. Appendicitis	Right lower paramedian incision. Very inflamed and swollen appendix removed, which was perforated accidentally in course of operation, with escape of free pus into peritoneum. Stab drain in right iliac fossa	10 g. sulphanilamide	Interrupted by persistent temperature	First intention	36 days
37	16, F.	Four days' abdominal pain, vomiting, etc. Appendicitis	Right paramedian incision. Very inflamed appendix removed. Some free fluid. Stab drain in right iliac fossa	10 g. sulphanilamide	Convalescence interrupted by wound infection and probable peritonitis. Subsequent recovery	Subsequent healing poor. Breakdown of lower part of main wound. Had to be reopened and drained	36 days
38	38, F.	Long history of attacks of abdominal pain, menorrhagia.	Laparotomy—right paramedian incision. Bilateral tubo-ovarian	20 g. sulphathiazole into pelvis	Drainage from pelvis gradually less	First intention	25 days

					recovery	wound. Had to be reopened and drained	
38	38, F.	Long history of attacks of abdominal pain, menorrhagia. Suddenly became acute. Diagnosed as pelvic abscess due to salpingitis	Laparotomy—right paramedian incision. Bilateral tubo-ovarian abscesses found. Both tubes and ovaries removed. Large quantity of free pus evacuated. Large drain into pelvis	20 g. sulphathiazole into pelvis	Drainage from pelvis gradually less	First intention	25 days
39	39, M.	Twenty-four hours' abdominal pain and vomiting. Diagnosed as obstruction	Right paramedian incision. Diagnosis confirmed, terminal ileum being obstructed by long appendix wound round it. Appendix very inflamed. Appendix removed. Obstruction relieved	10 g. sulphathiazole in peritoneum	Uninterrupted recovery	First intention	23 days
40	58, M.	Admitted for investigation of rectal bleeding. At sigmoidoscopy pelvic colon accidentally perforated	Immediate laparotomy. Perforation found and sutured and contents of large bowel cleared from pelvis. Drainage of pelvis	10 g. sulphanilamide	Uninterrupted recovery. Bleeding found to be due to piles	First intention	40 days
41	56, F.	History of forty hours' general abdominal pain, also in right iliac fossa. Abdomen distended	Right lower paramedian incision. Appendix normal. Gall-bladder found to be gangrenous and full of pus. Incision extended. Gall-bladder removed. Drainage right flank	10 g. sulphanilamide	Convalescence good except for bladder infection	First intention	20 days
42	40, F.	Three days' abdominal pain in lower abdomen. Diagnosed as appendicitis ? pelvic abscess or salpingitis	Right lower paramedian incision. Burst appendix, with abscess found. Appendix and adherent omentum removed. Large stab drain	25 g. sulphapyridine in abdominal cavity	Although patient very ill, she made a good recovery except for persistent temperature which was due to persistence of drainage. This subsequently dried up	First intention	41 days
43	65, F.	Twenty hours' abdominal pain, vomiting. Obese lady. Pain on deep pressure in both iliac fossæ. Diagnosed as retrocæcal appendicitis	Right lower paramedian incision. Extremely swollen and inflamed appendix which had ruptured into its own mesentery. Pus was spilt during the operation, contaminating the peritoneal cavity. Abdomen drained	16 g. sulphapyridine	Uninterrupted recovery	First intention	17 days
44	20, M.	Four days' abdominal pain. Diagnosed as acute appendicitis	Gridiron incision. Extremely inflamed ruptured appendix removed with difficulty. Free pus in abdominal cavity. Abdomen drained	10 g. sulphapyridine	Excellent recovery	Slight discharge from wound, but subsequent recovery	Up 10 days after operation, but retained in hospital 21 days owing to Naval routine
45	19, M.	Three days' abdominal pain. Diagnosed as acute appendicitis	Gridiron incision. Very inflamed gangrenous appendix with free pus found. Appendix removed. Pus cleared out from abdominal cavity. Abdomen drained	10 g. sulphapyridine	Excellent recovery	First intention	Up tenth day, but retained 22 days owing to Naval routine
46	22, F.	Thirty-six hours' abdominal pain, vomiting, etc. Very rigid abdomen. Diagnosed as appendicitis and probable peritonitis	Right paramedian incision. Perforated appendix, with peritonitis. Drainage in right flank	15 g. sulphapyridine	Uninterrupted recovery	First intention	11 days
47	10, F.	Six days' abdominal pain. Two days' vomiting, diarrhœa. Extremely ill and toxic child. Abdomen distended and tender all over. Diagnosed as appendicitis with peritonitis	Right lower paramedian incision. Extreme amount of free pus and inflamed bowel. Appendix removed and abdomen drained	25 g. sulphapyridine	Good, except for persistent temperature, for which no apparent cause could be found except peritoneal inflammation. This gradually settled	First intention	32 days

grave trouble than in gross contamination with pus already present. In the surgery of the large bowel, the problem of how to overcome or prevent the onset of gross infection in cases of accidental or unavoidable contamination—for example, in resection of the colon for cancer, with an anastomosis of the cut ends—has not been solved. In the resection of any portion of the alimentary tract from stomach to rectum a subsequent anastomosis may leak and cause peritonitis, and any method which will help to prevent this will be useful. Varco et al. (1941) pointed out that it was difficult to prevent leakage in internal anastomosis in dogs, a 25 per cent leakage rate occurred, and there was a 20 per cent mortality rate from this cause in the Mann-Williamson operation. When in their experiments they placed crystalline sulphanilamide in powder form around the suture lines at the time of operation, the mortality rate from leakage and peritonitis fell to nil; 37 such successful operations were performed, a total of 6 g. only of the powder being placed around the anastomotic line. Autopsy showed all suture lines well sealed with fibrin and the rest of the peritoneum in a normal state.

Garlock and Seley (1939) state that peritonitis is the chief cause of death, and remark on the greater safety of multiple-stage procedures. Methods of producing peritoneal immunity using sera, vaccines, amniotic fluid, etc., have all been unsuccessful. At the time of operation on colon cancers they made cultures of pericolonic tissue, bowel wall, and mucosal surfaces, and found that the predominant organisms were hæmolytic streptococci and *B. coli*; 21 cases were treated pre-operatively with sulphanilamide by mouth, and at subsequent operation it was found that the hæmolytic streptococci were absent and that subsequent soiling of the peritoneum at operation did not produce so serious results, and healing was exceedingly good.

It appears that in intraperitoneal chemotherapy we have a safeguard against peritonitis from leakages at suture lines, provided that the operation is performed in the complete absence of obstruction (which all surgeons agree should receive primary relief by some form of decompression operation), and that due regard is given to a careful method of suture in performing the anastomosis. Careful powdering of the anastomosis with sulphapyridine and the instillation of a suspension of the drug into the peritoneal cavity appear to obviate infection should leakage occur. All the inevitable minor contaminations will be controlled likewise, althought it is doubtful if such minor contamination is of serious import. Varco et al. (1941) advocated primary resection and anastomosis in cases of colonic cancer, using sulphapyridine by mouth prophylactically.

Wilensky (1942) records several cases of accidental peritoneal contamination with the contents of the large bowel or small gut during resection with no evil effects after the use of intraperitoneal sulphanilamide. I record here three personal cases all requiring resection of the large bowel, in which gross fæcal contamination occurred, which will illustrate the action of sulphapyridine in preventing subsequent peritonitis. *Case* 1 also illustrated this action.

Case 9.—A woman, aged 43, was admitted on Oct. 30, 1942, diagnosed as large-bowel obstruction due to intussusception. The illness started four days previously with general abdominal pain, marked diarrhœa and colic, with extremely frequent bowel actions and discharge of mucus. The symptoms became worse the day before admission and a large quantity of blood was passed. Apparently the illness began as an acute gastro-enteritis, prevalent in her home district at the time. Her general condition was good, there was no vomiting, no dehydration, and the blood-pressure was 120/90 mm. Hg. The abdomen was distended, especially over the descending colon, where a big mass was felt. There was also a mass which could be felt per rectum about 3 in. from the anus, and blood and mucus were escaping. The same night the abdomen was opened through a right paramedian incision and an enormously long engorged pelvic colon presented, with blackened gangrenous outer coats and some free fluid. The descending and upper parts of the pelvic colon had intussuscepted into the lower parts of the pelvic colon. The mesentery was extremely œdematous. At the pelvirectal junction, as soon as it was handled, the mesentery split away. An effort was made to reduce it, but the outer bowel coats immediately split for almost their whole length in the long axis, which enabled reduction to be attained. This left about 3½ ft. of torn gangrenous large bowel, mostly sigmoid colon, ending at the upper end of the rectum. A rapid resection of the gangrenous bowel was done and a modified Hartmann operation performed. The upper end of the rectum was closed and the lower end of the descending colon brought out into the left inguinal fossa as a permanent colostomy; 15 g. of sulphapyridine in saline was placed in the cavity and the wound lightly powdered. The patient stood the operation well and made an uninterrupted recovery, being discharged convalescent one month after operation.

Case 10.—A man, aged 54, admitted with intestinal obstruction due to a string cancer of the sigmoid. This was relieved by a preliminary cæcostomy. A second operation for resection of the growth was performed three weeks later, the growth and an ample portion of healthy bowel on either side being resected and an end-to-end anastomosis being performed by Mr. Joll. Peritoneal contamination occurred at operation and the suture lines were carefully powdered and 15 g. of sulphapyridine was placed in the peritoneal cavity. The patient made an uninterrupted recovery.

Case 11.—A woman, aged 48, was operated on by Mr. Joll in April, 1941, when a Hartmann operation for removal of cancer of the pelvirectal junction was done, followed by an excellent recovery. As there were no signs of recurrence fifteen months afterwards, it was decided to do a reconstitution of bowel continuity. At this operation, also performed by Mr. Joll, the colon was brought down and telescoped through the opened-out rectal stump on the Hochenegg principle, and the colon stitched all round to the rectal stump; 15 g. of sulphapyridine was placed in the cavity and the junction carefully powdered. The junction was drained through the old colostomy opening. An uninterrupted recovery was made with excellent results.

The method has also been employed in two primary resections of the right side of the colon for cancer of the cæcum and ascending colon. The above are representative cases, and we are now using the method in all cases of resection of the large bowel.

SUMMARY

1. No method of effectively combating peritonitis by a direct attack had been devised before the introduction of the sulphonamide drugs, which are successful in a large majority of cases if used intraperitoneally.

2. Diversity of bacterial flora and the presence of a large quantity of free pus interfere with the action of the sulphonamides in peritonitis.

3. Sulphanilamide and sulphapyridine appear to be the drugs of choice, and sulphapyridine shows the slowest absorption rate and the lowest toxicity of any so far employed.

4. On an average 15 g. is the dose of the sterilized powder recommended, but 25 g. or more may be inserted if profuse suppuration is present.

5. Contaminated wounds treated with an emulsion of the sulphonamide powders will heal by first intention in the large majority of cases.

6. Intraperitoneal chemotherapy should now be included in the armamentarium of all emergency surgeons. This is borne out by the reports showing a fall in the mortality rate of appendicitis and its complications and other acute abdominal conditions when it is employed.

7. Encouraging results appear to accrue from its use in intestinal obstruction necessitating bowel resection, but further investigation is necessary.

8. The whole course of large-bowel surgery may be altered by the use of intraperitoneal chemotherapy, and axial anastomosis become a safe method and that of choice in reconstituting bowel continuity.

9. Care in diagnosis, pre- and post-operative treatment, and technique are essential, and chemotherapy is but an adjunct to these.

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SHOCK: A CONSIDERATION OF ITS NATURE AND TREATMENT*

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Peripheral vascular collapse due to a reduction of the effective blood-volume may occur in several ways from a great variety of causes. For this reason the subject of shock is particularly complex, and has been rendered more so by a vast amount of ingeniously devised experimental work which supports this or that theory of its nature. A flood of research, stimulated by the outbreak of the present war, has complicated the subject still further. This paper is presented as a résumé of both old and new facts upon which treatment and further research is being based in this Unit.

It is of interest that although the study of traumatic shock received its first great impetus during the last war, one of the most accurate and far-seeing inquiries into the nature of the problem appeared in the first volume of the British Journal of Surgery in 1913. In that paper, A. Rendle Short, of Bristol, England, pointed out the inadequacies of the current theories, showed that these were not in accord with observed facts, and, largely by tempering the experimental studies of others with sound clinical observations, formulated a comprehensive conception of shock far in advance of its time. Attention is called to this important but seldom quoted paper, because now, as then, much error will be avoided if clinical observations and results are made the principal criteria by which all advances in this field are judged.

DEFINITION AND CLASSIFICATION OF SHOCK

The mechanisms of shock are so complex and so variable that precise definition is difficult. Harkins (1941) describes the condition as "a progressive vasoconstrictive oligemic anoxia". This is a concise and excellent definition for a certain stage of shock, but it excludes the neurogenic phases. Similarly, the definition proposed by Moon (1938) "a circulatory deficiency characterized by decreased cardiac output, decreased blood-volume, and by increased concentration of the blood", eliminates hæmorrhage from the syndrome. Because of these difficulties it has been suggested that shock be described in clinical terms as a state manifested by ashen-grey pallor, a weak, rapid, thready pulse, shallow respirations, and a low blood-pressure. But, like the Hippocratic facies in peritonitis, these are late and unfavourable signs. Shock should be anticipated, recognized, and treated before it becomes so severe. A definition is needed broad enough to include the earliest manifestations, yet sufficiently precise to exclude many conditions which are now loosely referred to as 'shock'. An international committee could clarify this problem by establishing a generally acceptable definition and classification.

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Classification of Shock

Neurogenic Shock:
Primary shock; Nervous shock; Syncope.

Vasogenic Shock:
Histamine shock; Toxic shock.

Hæmatogenic Shock:
Traumatic shock; Secondary shock; Surgical shock; Oligemic shock.

Decompensated Shock:
Late shock; Advanced shock.

Shock can be defined simply as "a state of actual or impending peripheral circulatory failure due to a reduction of the effective blood-volume which is not primarily cardiac in origin". This definition is essentially the same as that advanced some years ago by Cannon (1923), and later by Blalock (1934). The insertion of the phrase, "not primarily cardiac in origin" excludes the cardiogenic type of shock described by Blalock (1940). This seems an advantage, since Stead and Ebert (1942) have shown that the clinical appearance of shock which sometimes develops in cardiac patients is the result of a decreased cardiac output due to heart failure, and not to a decreased venous return to the heart. Because such cases present entirely different problems in therapy, the term 'shock' should be restricted to conditions in which the decreased cardiac output is due to a diminished venous return.

The effective blood-volume may be reduced actually by a loss of fluid from the circulation, or relatively by an uncompensated increase in the size of the vascular system. The vascular system may increase in size because of vasodilatation, neurogenic in origin, or as a result of direct injuries to arterioles or capillaries. Accordingly the shock syndrome may be divided arbitrarily into three main groups: *neurogenic*, caused by widespread vasodilatation without primary capillary injury; *vasogenic*, arising from direct injury to the walls of the capillaries; and *hæmatogenic*, the result of a primary loss of fluid from the circulation (Blalock, 1940).

Neurogenic Shock.—Neurogenic shock was formerly referred to as primary shock. A high spinal anæsthesia produces this state. The paralysis of sympathetic tone, both arterial and capillary, which ensues, causes a redistribution of

blood with pooling in the lower half of the body, a fall in arterial pressure, and temporary collapse. There is no capillary injury and no loss of fluid from the circulation. As the anæsthesia wears off a normal circulatory state is restored. The exact mechanisms which produce neurogenic shock are not known, but are thought to be similar to those which result in fainting, and are probably as variable. Psychic influences, extreme fright, and pain are of importance, although their roles are little understood.

There is no evidence that neurogenic factors alone result in advanced shock. When death occurs on a neurogenic basis it is probably caused by reflex vagal inhibition of the heart, and should not be considered as shock. In theory, a prolonged loss of vasoconstrictor tone can result in the following sequence of events : a fall in arterial pressure, a lowered venous return to the heart, a decrease in cardiac output, and finally a stagnant anoxia with capillary injury, loss of fluid from the circulation through damaged capillaries, and actual reduction of the blood-volume. Phemister (1942) has produced this syndrome experimentally by prolonged stimulation of the carotid sinus.

Clinically, neurogenic shock is manifested by pallor, sweating, and hypotension. Although the patient may appear seriously ill, the pulse is slow and fairly full rather than rapid or thready, and the extremities seem less cold than in advanced hæmatogenic shock. Recovery is usually prompt unless there are associated vasogenic or hæmatogenic factors. Although rare as a cause of death, neurogenic complications are of importance in other forms of shock (Ebert et al., 1941 ; McMichael, 1942 ; Wallace and Sharpey-Schafer, 1941).

Vasogenic Shock.—The classical example of vasogenic shock is histamine intoxication. When histamine in appropriate doses is injected into an experimental animal, the principal effect is direct injury to the capillaries, as a result of which constrictor tone is lost and arterial pressure falls. Subsequently, as the venous return to the heart diminishes, the cardiac output is reduced. In addition, there is, to a certain extent, a loss of fluid from the circulation through the damaged capillaries, a slowly progressive hæmoconcentration, and finally an actual reduction of the blood-volume, with stagnant anoxia, further capillary injury, and death. The actual reduction of the blood-volume is not marked. It occurs comparatively late and the fluid is lost into previously normal tissues throughout the body rather than into a local area of injury.

Although vasogenic shock is fairly well exemplified by histamine intoxication in the experimental animal, the exact clinical conditions belonging in this category are not clear. Various forms of shock, in which ' toxæmia ' is thought to play a role, such as the later stages of severe burns, certain forms of drug poisoning, the peripheral circulatory failure which sometimes accompanies severe infections, and anaphylactic shock, are all loosely placed in this category. Thus, at the present time there are included many types of collapse, the exact nature of which is not known, but in which primary capillary injury can reasonably be thought to play the dominant role.

Hæmatogenic Shock.—Hæmatogenic shock is the result of an actual loss of fluid from the circulation. This may occur as plasma in burns or crushing injuries, as blood in hæmorrhage, or as water and electrolytes in severe vomiting, diarrhœa, or high fever. Although there are many important differences among these types, a factor common to all is an immediate reduction of the blood-volume. This is followed by two compensatory phenomena : the movement of available extracellular tissue fluid into the blood-stream, and vasoconstriction. The former attempts to restore the blood-volume, but since red blood-cells and proteins are not as readily available as fluid, hæmodilution occurs. The latter maintains the arterial pressure despite the reduced blood-volume and a diminishing venous return and cardiac output. This compensatory vasoconstriction, though beneficial in maintaining an adequate circulation to vital centres, may lead to tissue anoxia and capillary injury in the areas deprived of blood by the vasoconstriction (Freeman, 1935). As the blood-volume is further reduced the arterial pressure falls, despite continued vasoconstriction, and a stage of stagnant anoxia with generalized capillary and tissue injury supervenes. Finally, as a consequence of the capillary and tissue injury, fluid may be lost from the circulation, not only at the site of injury but throughout the viscera.

This sequence of events represents in the simplest terms the course of hæmatogenic shock, regardless of cause. Actually, the problem is not this simple because of certain variables purposely omitted from the discussion for the sake of clarity. These include the effects of acute hypoproteinæmia, hæmoconcentration, adrenal insufficiency, and the action of hypothetical toxins, all of which may complicate the shock syndrome. These variables probably do not alter the fundamental nature of hæmatogenic shock, but when present they influence the rate of progression to a state which will be discussed below under the heading of ' decompensated shock '.

Clinically, all forms of uncomplicated hæmatogenic shock are characterized by the fact that the blood-pressure may be normal, and if too much reliance is placed upon this sign, a state of severe shock may be overlooked. This is particularly true of the more slowly progressive cases in which compensatory mechanisms become established.

Decompensated Shock.—The common denominator in hæmatogenic shock, regardless of the type of fluid lost, is an actual reduction of the blood-volume. Once this occurs, a train of secondary events is set in motion, which, although the rate of progression and the exact sequence

of events may vary in the different types of shock, leads to a state which might be termed 'secondary' shock, meaning secondary to a prolonged reduction of the blood-volume. However, because the term 'secondary shock' has been used for so many years as synonymous with 'traumatic shock' or 'surgical shock' and because it fails to imply the advanced and perhaps irreversible character of the syndrome, the term 'decompensated shock' is suggested. The fact that the factors, there should be no difficulty in distinguishing the two conditions on clinical grounds by the time factor as well as the generally poorer condition of the patient in decompensated shock. Decompensated shock, particularly if complicated by a general anæsthetic, often passes into an irreversible stage in spite of therapy.

Not only may the various types of shock lead one to another, and eventually to decompensated shock, but in any given patient more than one type may be initiating factors. The situation may be depicted diagrammatically as in *Fig.* 29. Failure to appreciate the interplay of the many variables which may contribute to the 'vicious circle' of shock has led to considerable controversy, certain aspects of which merit discussion and an attempt at clarification.

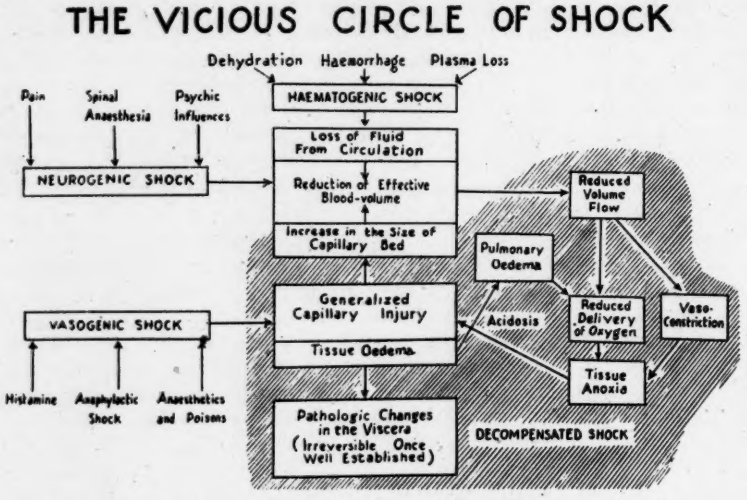

FIG. 29.—A diagrammatic representation of the many variables which may enter the shock syndrome. Such theoretical conceptions are useful in teaching, or as a basis for discussion, but it is not certain that the sequences occur exactly as represented.

THE CONTROVERSY ABOUT HÆMORRHAGE AND SHOCK

Some investigators have attempted to draw a sharp distinction between hæmorrhage and shock. In recent years this view has been especially championed by Moon (1938). From a practical point of view this is a great mistake. As Harkins (1941) says, "In clinical cases usually both whole blood and plasma are lost. After all it matters little what colour fluid is lost from the blood-stream, red or yellow". The problem resolves itself largely into a matter of semantics. If shock is defined as 'a state of actual, or impending, peripheral vascular collapse due to a reduction of the effective blood-volume', then, hæmorrhage must be included. Specifically it constitutes a particular form of hæmatogenic shock.

That there are important differences between simple hæmorrhage and shock associated with the loss of plasma which accompanies a severe burn, no one can question. In burns the reduction of the blood-volume is complicated from the beginning by hæmoconcentration, marked depletion of the total plasma protein, acidosis, gross destruction of tissue, and possibly adrenal cortical insufficiency. Thus, there is a very rapid progression from the early stages of hæmatogenic shock to fully established decompensated shock. On the other hand, in hæmorrhage, the reduction of the blood-volume is well tolerated unless it is maintained at a low level for a considerable period of time, or is complicated by other factors such as anæsthesia. Although there is some doubt as to whether a state of irreversible shock can be produced by hæmorrhage alone (Price et al., 1941), Blalock (1934) has observed hæmoconcentration, an unfavourable response to transfusion, and

word decompensation has been used specifically in relation to cardiac failure, does not vitiate its use in advanced shock, since the recent studies of Wiggers (1942) suggest that in this condition the factors which finally determine a fatal issue are cardiac in nature.

Decompensated shock is characterized by a lowered venous return, a diminished cardiac output, a low arterial pressure, decreased oxygen consumption, hypoproteinæmia, acidosis, and anoxia. Additional contributing or terminal factors, regardless of the original cause, may be progressive hæmoconcentration from loss of fluid through damaged capillaries, adrenal cortical insufficiency, hyperpotassæmia, and the action of toxins or metabolites from injured tissues. The summation of these factors leads to a death which is characterized pathologically by dilated and congested capillaries, capillary hæmorrhages, œdema, and degenerative changes in parenchymous tissues throughout the lungs, liver, kidneys, and gastro-intestinal tract.

Clinically, decompensated shock is manifested by ashen-grey pallor, a weak rapid thready pulse, shallow respiration, a cold moist skin, mental apathy, subnormal temperature, and a low blood-pressure. This is advanced, or late, shock. Although it may be simulated by an early stage of hæmatogenic shock complicated by neurogenic

histologic evidence of capillary injury as a result of uncomplicated hæmorrhage in unanæsthetized animals. Moreover, in practice the problem of hæmorrhagic shock is not that of simple hæmorrhage, but that of hæmorrhage accompanied by varying degrees of tissue injury from trauma, with plasma loss, variable neurogenic factors, and often the hazards of anæsthesia. In this situation the important and decisive factor is the loss of blood. Hæmoconcentration and hypoproteinæmia are not early or prominent factors, but eventually there develops a degree of shock which is characterized by all the usual features of this state, including the same post-mortem histologic changes. These facts justify the inclusion of hæmorrhage as a form of hæmatogenic shock. In military surgery it is the most important form.

HÆMOCONCENTRATION

In recent years there has been a renewed interest in, and considerable emphasis on, hæmoconcentration as an early sign of shock (Moon, 1938). It is of interest that the significance of hæmoconcentration was pointed out by Sherrington in 1893, and was used as a guide to prognosis during the last war (1923). When interpreted correctly it is a valuable sign, especially as a guide to therapy, but it is by no means invariably the earliest sign of shock. It is an early and invariable accompaniment of dehydration and loss of plasma, but it does not occur in neurogenic shock or hæmorrhage, and may develop comparatively late in conditions ascribed to vasogenic shock. Progressive hæmoconcentration in spite of adequate replacement therapy may occur in advanced shock. It is a variable finding and difficult to interpret when whole blood and additional plasma are lost simultaneously.

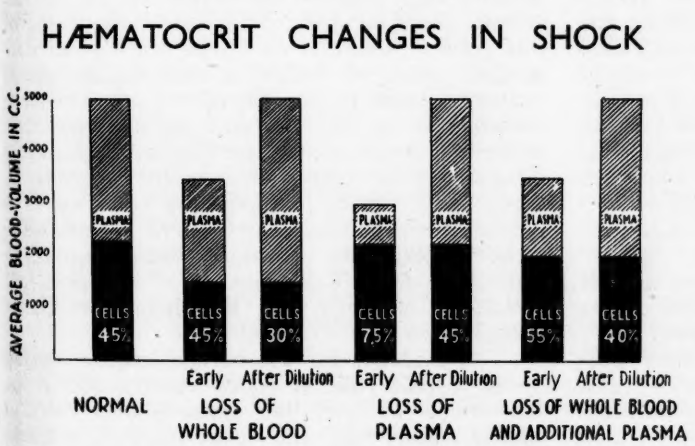

FIG. 30.—Possible variations of the hæmatocrit in shock (*after Harkins*).

The possible variations of hæmatocrit readings have been well described (Harkins, 1941; Mahoney and Howland, 1943) (*Fig.* 30). In the early stage of acute hæmorrhage there is no change in the concentration of the blood. Later, as hæmodilution occurs, there is a gradual fall in the hæmatocrit. If fluid is given to replace the loss of blood, the hæmatocrit falls rapidly. When plasma rather than blood is lost there is early and marked hæmoconcentration, the hæmatocrit rising to 60 or 75. Later, after hæmodilution occurs, or infusions have been given, it returns to normal. When whole blood and additional plasma are lost simultaneously, as in a crushing injury associated with hæmorrhage from another wound, the initial changes in the hæmatocrit are in the direction of concentration, but following therapy with fluid, because of the loss of blood, the late findings indicate hæmodilution. An appreciation of these facts is of fundamental importance, and their application in the treatment of shock is dependent upon a close correlation of the laboratory findings with the clinical history.

THE PULSE AND THE BLOOD-PRESSURE IN SHOCK

The unreliability of the blood-pressure in shock was emphasized in 1919 by Gesell and has been re-emphasized by many workers in this field. This does not mean that it is a useless sign. Indeed, Kekwick, Marriott, Maycock, and Whitby (1941) found it to be the most valuable single sign in their experience with air-raid casualties. Once again it is a matter of correct interpretation in the light of all available evidence. If there are factors which produce a loss of vasoconstrictor tone, or generalized capillary injury, the arterial pressure will be low. Thus it is low in neurogenic shock without necessarily being of grave import. If there is an actual reduction of the blood-volume from loss of blood or plasma, there may be a low pressure at first from neurogenic factors, and if the shock is severe there may be no reaction from fall in pressure. Usually, however, after pain and fear have been relieved, compensatory vasoconstriction will return the arterial pressure to normal, or even above normal levels despite a continued reduction of the blood-volume. This phase of temporary hypertension, sometimes associated with variations in the blood-pressure (Traube-Herring waves) frequently occurs in experimental shock. It is less obvious clinically, but McMichael (1942) noted it in his study of a series of air-raid casualties. Finally, the blood-pressure is low in decompensated shock regardless of cause.

When confronted with a low blood-pressure one must decide on the basis of the available evidence, whether it is the result of neurogenic, a combination of neurogenic and early hæmatogenic,

or decompensated shock. Conversely, a normal or even high blood-pressure must not lead one to overlook hæmatogenic shock at a time when replacement fluid may be urgently required, and, if given promptly, decompensated shock averted. Determinations of the hæmatocrit and plasma protein may be of value in trying to interpret the significance of a low blood-pressure, but the most important evidence is obtained from a careful evaluation of the clinical history.

Hill, McMichael, and Scharpey-Schafer (1940) found that a continued elevation of the pulse-rate, even after adequate replacement therapy, was not an unfavourable sign in shock. Conversely, they, and others, noted very slow rates after severe hæmorrhage (Ebert et al., 1941; Wallace and Sharpey-Schafer, 1941). However, if these facts are taken into consideration, careful repeated and thoughtful evaluation of the pulse, noting not only the rate, but the character and the quality, is a most helpful guide to prognosis and therapy. It is one procedure which the surgeon can always do, anytime and anywhere, and to the experienced it gives information of great value.

CAPILLARY INJURY AND THE PATHOLOGY OF SHOCK

There is no doubt that local increased capillary permeability occurs at the site of extensive injuries. It has become axiomatic, however, that generalized capillary injury plays a major role in the vicious circle of shock. The actual evidence for this rests largely upon the established causal relationship between anoxia and increased capillary permeability. The importance of anoxia and its effect on the capillary bed in shock has been emphasized by many investigators (Harkins, 1941). Recently Root and Mann (1942) observed capillary dilatation and stasis in the liver and mesentery secondary to a local loss of fluid at the site of an injury. No positive evidence was found for the liberation of a toxic substance causing immediate capillary damage in the types of shock studied. Fine and Seligman (1943), in a study of the behaviour of proteins 'tagged' with radio-active sulphur, found evidence of capillary permeability only in the very late stages of experimental shock due to hæmorrhage.

That a generalized abnormal capillary permeability occurs in the terminal stages of shock seems well established. This is quite a different thing from the extreme position taken by Moon (1938), who describes a wheal as shock in miniature, and holds that, regardless of cause, capillary injury is a primary factor. Apart from assumption, the principal evidence which Moon presents for generalized capillary injury as a fundamental factor in all forms of shock, are his morphologic studies of the viscera of animals who have died in shock. However, if the time factor is taken into consideration, the histologic changes in shock due to burns and trauma are essentially the same as in hæmorrhage. Moreover, these develop only after the blood-volume has been reduced by a local loss of fluid at the site of injury, and appear, therefore, to be a secondary rather than a primary phenomenon (Dunphy et al., 1941).

The situation may be summarized as follows: (1) By definition there is no capillary injury in neurogenic shock. (2) By definition capillary injury is the fundamental factor in vasogenic shock, but at present there is no convincing proof that capillary injury occurs as a primary phenomenon in any of the clinical states classified as vasogenic shock. Therefore, final judgement must be withheld until the situation is clarified by further study. (3) The principal argument centres about hæmatogenic shock, in which the available evidence indicates that capillary injury occurs as a late and purely secondary phenomenon, the principal evidence for which are the pathological changes which occur throughout the viscera. Although these late changes are interpreted to be a consequence of capillary injury, it is quite possible that generalized tissue injury, especially in highly specialized organs such as the brain, liver, or adrenals, occurs long before the capillaries are damaged. The use of a tourniquet in surgical operations is ample evidence that the capillaries of the leg can withstand ischæmia for longer periods than the tissues of the liver or brain. Indeed, by future study, the response of the capillaries to injury may prove to be secondary to tissue injury.

THE ROLE OF THE ADRENAL GLAND

A discussion of all the evidence, for and against, both hyper- and hypo-activity of the adrenal gland, in shock is not within the scope of this paper. There is no doubt that the adrenal medulla exerts an action in hæmatogenic shock by contributing to the generalized compensatory vasoconstriction which accompanies a reduction of the blood-volume. Since this action primarily safeguards vital centres which might otherwise be deprived of blood, it should be regarded as a homeostatic phenomenon. There is not sufficient evidence to consider adrenal medullary activity as either a primary cause or a principal secondary factor in the peripheral circulatory failure of shock.

The evidence for the adrenal cortex playing an important role in shock centres about the following: a shock-like state follows bilateral adrenalectomy in the experimental animal; adrenalectomized animals are more susceptible to shock following trauma than normal animals; certain pathological changes appear in the adrenal gland in shock, especially in burns; and the course of clinical and experimental shock has been reported to be favourably altered by a number of investigators using a variety of adrenal cortical hormones. On the surface this looks like an imposing array of evidence, but actually there is little solid proof for the action of the adrenal cortex as a primary factor.

Until further evidence is available the role of the adrenal gland and the value of adrenal cortical extract in the treatment of shock should be regarded as controversial subjects requiring further study (Mahoney and Howland, 1943).

THE THEORY OF TOXÆMIA

At present there is no proof of a specific toxin as a primary factor in neurogenic or hæmatogenic shock. The nature of vasogenic shock implies that the causative agent produces a specific injury to the capillaries and hence quite properly can be referred to as a 'toxin'. Histamine shock is a good example, but with the possible exception of anaphylactic shock there is not sufficient evidence to place any clinical states categorically in this classification. Thus Ebert and Stead (1941) have shown that the circulatory failure of severe infections is not associated with hæmoconcentration or a decrease in plasma volume. On the other hand, in decompensated shock, particularly that which follows burns or crushing injuries, the possibility that products of injured tissue enter the circulation and play a role in the irreversible stage of shock cannot be excluded. That an irreversible state may develop is undoubted. It has been noted clinically by many observers. Experimentally, it has been shown that complete restoration of the blood-volume by replacement therapy is without avail in the late stages of severe burns (Dunphy and Gibson, 1941).

The observations of Duncan and Blalock (1943) demonstrate the irreversible character of the shock which follows release of a tourniquet from an ischæmic traumatized limb, and the studies of Bywaters (1941) on the crush syndrome in man afford ample evidence that the products of muscle catabolism may enter the circulation. Of especial interest and importance is the identification of the chemical nature of a shock-producing factor isolated from normal striated muscle by Green (1943). These observations represent a real advance in the search for a toxic factor. However, at present direct applicability to the problem of shock in man is limited to additional emphasis on the hazards of the use of a tourniquet to control bleeding in damaged limbs.

Govier (1943) has shown that animals which have been given large doses of thiamine have an increased resistance to shock induced by hæmorrhage. While Maycock (1943) has been unable to confirm these observations, this approach to the problem of late shock as one of altered cellular metabolism may prove fruitful. Also of interest in this respect are the experimental observations of Mylon and his co-workers (1943). They have found that injections of small amounts of agents such as methylene blue or sodium succinate, which may have an effect on tissue respiration, will not only produce a rise in arterial pressure in late shock, but when given with replacement fluid appear to increase the survival rate over that obtained with fluid alone.

THE DIAGNOSIS OF SHOCK

The invaluable studies of air-raid casualties in the early years of the present war show that chief reliance must be placed on experience and sound clinical judgement in recognizing the various stages of shock, and in evaluating the effects of, and indications for, treatment (Grant and Reeve, 1941; Kekwick et al., 1941). If a patient is admitted in apparent collapse, with a blood-pressure which is hardly measurable, but with warm extremities and a pulse which is only moderately elevated and of fair quality, and if, furthermore, the history reveals that although thrown from a vehicle he landed on soft ground, and no evidence can be found for fracture or other grave injuries, he cannot be considered to be in advanced or decompensated shock. Neurogenic shock is more probable, but one must be guarded in a prognosis until further observation excludes the possibility of intra-abdominal injury with internal bleeding. It must be remembered that in hæmorrhage vasovagal reflexes may produce a slowing of the pulse quite similar to that seen in ordinary syncope. Assuming no such factors, such a patient will recover promptly, and to ascribe recovery to the use of some adrenal cortical hormone is, to say the least, unsound.

On the other hand, if a patient is seen with a compound fracture of the femur, multiple lacerated wounds, and a possible abdominal injury, one must not overlook established hæmatogenic shock because the blood-pressure is normal and the pulse-rate is only 110. Every effort to appraise accurately the state of this patient's circulation must be made. It is under such circumstances that determinations of the hæmatocrit and serum protein are often helpful. These determinations, while by no means indispensible, are an aid to early diagnosis and may be of value in determining the type and amount of fluid replacement required. This is particularly true in hæmatogenic shock when the fluid loss is severe and chiefly of one type.

It must be emphasized that a changing hæmatocrit is of far more value than a single determination. Progressive hæmoconcentration in spite of therapy is a sign of decompensated shock. Even in the presence of hæmorrhage, repeated determinations of the hæmatocrit may be helpful. Determinations made after replacement therapy with plasma will show a marked reduction, and often give evidence of the severity of the initial blood-loss. Continued hæmodilution after transfusion with blood may indicate continued bleeding in doubtful cases.

A hæmoglobin determination by the Sahli technique will afford sufficient information for clinical purposes. Nor is it essential to have any of these laboratory procedures. They should be looked upon as supplementary and confirmatory

procedures, and of value in the study of shock. But if one knows from the history that a patient has lost a litre of blood, one need not wait for laboratory data to transfuse. Common sense and ordinary clinical acumen and thoroughness will save more patients and provide better shock therapy than all known laboratory procedures.

TREATMENT OF SHOCK

Uncomplicated neurogenic shock probably would always recover without treatment, but recovery seems to be hastened by rest with the head slightly dependent, sedation, and warm drinks, and thus the possible effects of associated injuries are more readily evaluated. Failure of neurogenic shock to improve promptly under such measures should immediately stimulate a further search for unrecognized injuries. Whenever there is capillary or tissue injury, local or generalized, the use of saline may be dangerous, but in neurogenic shock there is no capillary injury and the factors which bring about an increase in the size of the vascular bed are of short duration. A saline infusion increases the blood-volume temporarily, but escapes from the circulation as the vascular tone is restored to normal. It is especially useful in treating the hypotension of high spinal anæsthesia.

The treatment of vasogenic shock remains an hypothetical problem since at present it is not clear precisely what clinical conditions belong in this category. It appears evident that measures directed toward removal of causative agents are of greater importance than measures designed to improve the peripheral circulatory failure (Ebert and Stead, 1941).

The treatment of hæmatogenic shock falls into three categories: (*a*) General supportive measures; (*b*) Restoration of the blood-volume by the most suitable means available; (*c*) Supplementary measures of doubtful value.

General Supportive Measures.—The time-honoured measures of the Trendelenburg position, morphine, and the application of heat are open to certain criticisms in the light of newer knowledge. The so-called ' shock position ' is of value in neurogenic shock and as an emergency procedure in hæmatogenic shock until the blood-volume has been restored by replacement therapy. Since it causes a certain degree of cardiac and respiratory embarrassment it should not be used to an extreme degree. If the head is very slightly below the horizontal, full benefit from this position will be obtained with little of the disadvantages. After restoration of the blood-volume by replacement therapy there is no need for the continued or routine use of the head-down position.

It is now well established that heat, as furnished by many hot-water bottles wrapped up in blankets, or by the so-called ' shock cradle ', is detrimental. It increases the metabolism of peripheral tissues when available blood and oxygen are needed elsewhere. On the other hand, despite some suggestive evidence that cold may have a beneficial influence, there is no sound basis for its use. A common-sense attitude of maintaining normal body warmth should be adopted. The term ' prevention of exposure ' should be substituted for ' application of heat ' in the treatment of shock.

The value of morphine is unquestionable, but it is to be used to relieve pain and not as a routine procedure. The beneficial effects of morphine are due to its alleviation of factors contributing to neurogenic shock. When given repeatedly without indication it serves only to depress the respiratory centre and possibly aggravate an already existing anoxia.

The importance of promptly splinting fractures and extensive wounds before transportation of patients cannot be over-emphasized. It is as important as in the last war, and fortunately is fully appreciated.

Restoration of the Blood-volume.—If a man loses five litres of blood slowly over a period of hours he will die, and he will die of shock. If he is transfused with five litres of blood, and if these transfusions are given so that the blood-volume is maintained at all times, he will not die. This, in the simplest terms, is the treatment of hæmatogenic shock. Moreover, without blood or plasma, no amount of drugs, adrenal extract, or oxygen will benefit this patient.

So it is in all forms of hæmatogenic shock. The primary consideration is to maintain the blood-volume. No fluid, not even plasma, remains in the blood-stream. It is poured into the area of injury, not in the form in which it was given, but as diluted plasma. This is an extremely important fact which Beard and Blalock first presented in 1931. It represents one of the most important advances in our knowledge of shock. If the fluid is not replaced in the form in which it is lost, the various constituents of the blood may be washed out into the area of injury. For this reason the use of saline solutions in shock accompanied by loss of plasma may be dangerous. Although such solutions produce a temporary rise in the blood-volume, this is of short duration and results in such dilution of the blood that the serum proteins are quickly reduced to œdema levels. Moreover, as the fluid leaks out of the blood-stream as dilute plasma, it increases still further the rate of protein loss. As a consequence of protein depletion to œdema levels, fluid is lost not merely into an area of injury, but throughout the viscera, pulmonary œdema being an obvious manifestation. The use of saline infusions should be reserved, therefore, for those conditions in which shock is clearly neurogenic or the result of dehydration from loss of water and electrolytes.

In military surgery, the majority of cases of shock are either due to or complicated by hæmorrhage. Although as previously pointed out, determination of the hæmatocrit or hæmoglobin

after replacement with plasma may be helpful, reliance must be placed chiefly on the history and clinical examination of the patient. In general, if an infusion is needed at all, 1000 c.c. represents a minimum requirement. If the history and physical examination indicate a loss of blood or plasma or both, this should be started at once and given rapidly, the first 500 c.c. within ten to twenty minutes. If more than 1000 c.c. of plasma is required to bring about or maintain a response, 500 c.c. of whole blood should be given. With each additional litre of replacement fluid required, at least 500 c.c. of blood is given. If improvement is not obtained after 2000 c.c. of replacement fluid and there is a great demand for plasma and blood for other casualties, the situation should be reviewed and consideration given to the possibility that one is dealing with a hopeless case. On the other hand, if a favourable response occurs, there is practically no limit to the amounts which may be given to *maintain* the circulation.

In cases in which there is continued bleeding it is of vital importance not to delay essential surgery. It is useless to transfuse and delay. Preparation for surgery should be carried out as the shock is treated, and as soon as the arterial pressure rises to 90 mm. or 100 mm. Hg, or higher, the pulse slows appreciably, the extremities improve in warmth and colour, and the estimated fluid loss has been replaced, operation should be done, *but*, at the same time *therapy must be continued* until the bleeding is controlled and a good circulatory state maintained. In severe cases 5000–6000 c.c. or more may be necessary. Whole blood in addition to plasma is of vital importance in treating severe shock due to hæmorrhage, particularly when extensive surgery with prolonged anæsthesia is required. The use of plasma as a complete substitute for blood has proven singularly disappointing.

There are several useful ways of estimating the amount of plasma required in severe burns. The 'first-aid formula' of Harkins (1941) is especially useful. This calls for one pint of plasma for each 10 per cent of body area burned. Since this gives the total amount required it should be given over a period of about 12 hours. If a hæmatocrit or hæmoglobin estimation can be done the following formulæ are simple and valuable :

a. Plasma required $= \left(5 - \frac{500}{Hb_2}\right) \times 1000$, in which Hb_2 is the hæmoglobin observed after the burn (Black, 1940).

b. For each point the hæmatocrit is elevated above the normal of 45 give 100 c.c. of plasma (Harkins, 1941).

Both these formulæ should be familiar to those who treat the shock of severe burns. It is unwise, however, to place complete reliance upon them, and in addition to using them as a guide to requirements, the actual response of the patient to therapy should be used as an indication for additional requirements. In general, it is better to err on the side of too much rather than too little replacement when dealing with young subjects without cardiovascular disease.

Supplementary Measures.—These include such measures as hypertonic solutions, oxygen, coramine, and adrenal cortical extracts. The situation may be summarized by repeating that if a patient loses five litres of blood over a period of hours he will die in profound shock. If he is transfused with five litres of blood so as to maintain the blood-volume he will not die, and no other therapy is required to save his life. Moreover, without blood and plasma no amount of concentrated solutions, drugs, oxygen, or cortical extracts will save this man's life. This is not to say that these supplementary measures have no place in shock therapy, but in general their use has not been proven essential, and their place should be considered secondary to measures designed to restore the lost fluids by volume-for-volume replacement.

The recognized anoxia of shock would seem to make oxygen therapy essential, but the anoxia of shock is primarily circulatory and if the circulation is restored by transfusion there is little need for oxygen unless there are specific indications for its use, such as marked dyspnœa, cyanosis, air hunger, or specific disease or injury of the chest. Again, from a practical point of view the difficulties attendant upon properly administering oxygen, plus the discomfort caused the patient, may interfere with, or delay, more vital forms of therapy. It should be used whenever specifically indicated, but not as a routine.

Adrenal cortical extract may have a place in the treatment of severe burns as an adjunct to plasma infusions, but in general its use, as well as that of various drugs, should be viewed as largely experimental and certainly not of primary importance in the practical treatment of shock.

Highly concentrated solutions of plasma and albumin are also of doubtful value in the therapy of shock. As a means of providing large amounts of available protein in small packages for ease of transport, concentrated or dried preparations have a place in military surgery. This particularly applies to albumin, which is admirably suited for transportation because of its stability in a 25 per cent solution. Whether these preparations should be used in concentrated forms, however, is a matter for conjecture. It is possible that a single infusion of a concentrated protein solution given in the early stages of shock, in a patient in whom there is no marked dehydration, may mobilize additional fluid reserves more rapidly than normal and thus maintain the circulation until blood or plasma is available. In conditions such as severe burns, in which the local loss of fluid is enormous, concentrated solutions in addition to dilute isotonic fluid replacement may prove beneficial in limiting local œdema. On the other hand, it is obvious that if the loss of fluids is prolonged and severe, and especially

if there is associated dehydration, adequate replacement of the lost fluids cannot be accomplished with hypertonic solutions. The lost fluid must be replaced in the form in which it is lost, which means giving blood or dilute plasma, or both.

It should be obvious from the foregoing that there can be no adequate substitute for blood and plasma in the treatment of severe hæmatogenic shock. Inasmuch as any form of replacement fluid enters the area of injury diluted with plasma, and amounts of 1500 to 2000 c.c. represent minimal requirements, it is evident that a major portion of the original blood-volume must be replaced by the infusion. Although possibly suitable for maintaining the blood-volume, substitutes such as gelatin, pectin, isinglass, or even albumin will not provide the essential requirements of blood. Experimental studies with bovine albumin indicate its limitations in this respect in comparison with plasma (Dunphy and Gibson, 1943). All blood substitutes must be recognized, therefore, as mere expedients, used because of greater availability or ease of transport, as a means of maintaining the circulation until blood or plasma can be given.

SUMMARY

Shock is defined as "a state of actual, or impending, peripheral circulatory failure due to a reduction of the effective blood-volume which is not primarily cardiac in origin".

Depending upon the mechanisms involved, three types are postulated: *neurogenic*, a state of widespread vasodilatation without primary capillary injury; *vasogenic*, a consequence of a direct injury to the walls of capillaries; and *hæmatogenic*, the result of a primary loss of fluid from the circulation. The term *decompensated shock* is applied to the physiological sequences which follow a prolonged reduction of the effective blood-volume, regardless of the original cause or causes.

Particular emphasis is placed on the necessity for an evaluation of the entire clinical picture in recognizing the earliest stages of shock and in determining the need for, and the efficacy of, various forms of therapy.

The fundamental treatment of shock in military surgery resolves itself into the prompt replacement of blood with blood, and plasma with plasma; the limitations of blood substitutes and the secondary importance of all other forms of therapy are stressed.

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CHOLESTEATOMA OF THE PETROUS BONE

By JOE PENNYBACKER

FROM THE NUFFIELD DEPARTMENT OF SURGERY, OXFORD

PROGRESSIVE paralysis of the facial nerve is not a very common affection. When it does occur, pressure on the nerve by a neoplasm is a likely cause, and when the facial paralysis is accompanied by deafness and absence of the caloric responses on the same side, the tumour is commonly in the cerebello-pontine angle, e.g., an acoustic neurinoma. In other cases, the nerve may be subjected to pressure in its course through the petrous bone, and this report is concerned with three such cases recently encountered in the Nuffield Department of Surgery in which the lesion was found to be a cholesteatoma in the petrous bone.

CASE REPORTS

Case 1.—

HISTORY.—A medical practitioner, aged 42, was admitted to the Radcliffe Infirmary on May 12, 1941. In November, 1938, he was first aware of some right facial weakness, his attention being drawn to it by food collecting in the right corner of his mouth, and by his inability to whistle properly. Some weeks later the weakness was slight enough to have been missed in an examination for life insurance.

In February, 1939, three months after the onset of the facial weakness, he had an attack of otitis media on the right side. So far as he knew, he had never had any trouble with his ears before. After forty-eight hours of earache, the drum burst and there was a little blood-stained purulent discharge for a week. There had been no recurrence of pain or discharge, but from the time of this infection there had been a considerable deafness of the right ear. Although the patient was fully aware of the facial palsy during this illness, it was still slight enough to have missed detection by the aural surgeon who attended him.

It is difficult to say how long it took the palsy to become complete, but it was not until June, 1940 (at least eighteen months after the weakness was first noticed) that he sought advice about it. Probably the palsy had been fairly complete for some months before this, as the patient took rather an optimistic view of the affection and was loath to admit that the paralysis was ever complete.

ON EXAMINATION.—He was a healthy man and there were no neurological abnormalities, except a complete right facial paralysis, with some fibrillation at the right angle of the mouth. There was impairment of the sense of taste on the right side of the tongue. He was very deaf in the right ear: with a noise box in the left ear he could only hear loud shouts at 1 ft. in the right ear; the hearing in the left ear was clinically normal, but the audiogram showed some loss of high tones on the left side too. The Weber was referred to the right. A.C. was greater than B.C. on both sides, but there was some relative loss of bone conduction on the right side as compared with the left. Our otological colleagues identified this as a mixed type of deafness, and in any case it seemed out of proportion to the history of a mild otitis media and the appearance of the drum: the right drum was intact, but there was a small scar behind the handle of the malleus. The left drum was normal. The caloric responses were absent on the right side, but were normal on the left. Radiographs (*Fig.* 31) of the skull showed an erosion of the upper surface of the petrous bone medial to the mastoid antrum, but

Left *Right*

FIG. 31.—*Case* 1. Radiograph showing erosion of the superior surface of the right petrous bone.

no other abnormalities. The mastoid air cells were of about normal translucency.

The important negative findings were that the optic fundi and visual fields were normal, as were the pupils and external ocular movements. There was no sensory impairment in the trigeminal area and no abnormality in the functions subserved by the lower cranial nerves. In his limbs there was no dystonia, inco-ordination, or weakness, no abnormality of the reflexes, and no disturbance of gait. The cerebro-spinal fluid was normal as to pressure and content.

This patient was seen some months before he was admitted to hospital, and the findings of progressive facial palsy, deafness, and absence of caloric responses led to the provisional diagnosis of an acoustic neurinoma in the very early stages of its development. I was not familiar with the X-ray appearances, but Professor Cairns thought that these appearances and the clinical state were likely to be due to a cholesteatoma of the petrous bone.

AT OPERATION.—As there was no evidence of active mastoid infection, and as the radiographs suggested that the lesion should be accessible by way of the middle fossa, we operated on May 19, 1941, by the approach commonly used for section of the trigeminal root. The dura was elevated from the upper surface of the petrous bone without difficulty. There was an irregularly oval erosion of the petrous bone anterior to the arcuate eminence measuring about 1·2 cm. in its longer axis. The defect was filled with soft, cheesy white material which could be lifted out in little chunks with a blunt hook or a small spoon. An irregular cavity was cleared of this material, and the facial nerve could be seen bared up to the genu. It was intact but flattened. The bone forming the walls of the cavity looked normal, but a fragment removed for histological examination showed some thickening of the periosteum and chronic inflammatory infiltration.

PROGRESS.—The wound healed normally and the patient resumed his practice about a month after

operation. He has remained well for the ensuing two and a half years, but there has been no improvement in the facial palsy. The muscles have been treated with galvanism from the time of operation, and although they have retained both their bulk and contractility, there is no voluntary movement nor any response to faradism. The deafness is unaltered, and there has been no recurrence of the earache or discharge.

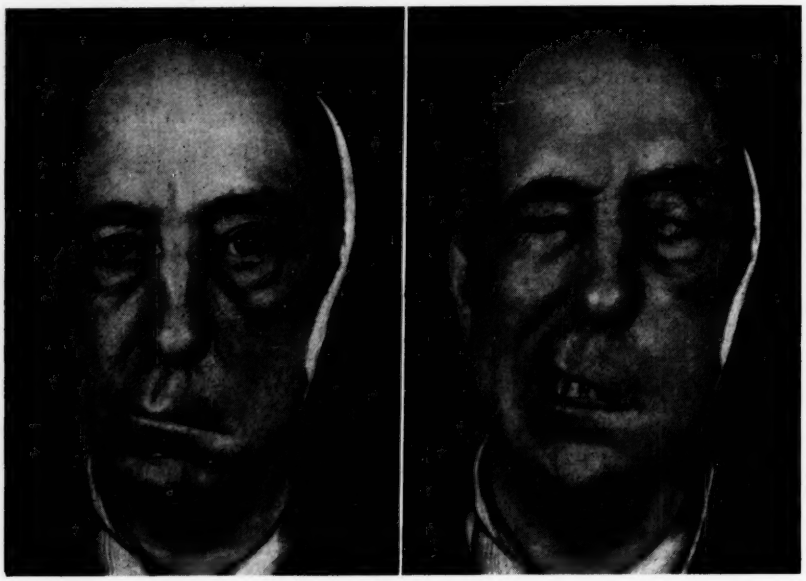


FIG. 32.—*Case* 2. Photographs taken five days after operation, showing left facial paralysis as before operation.

Case 2.—This case was rather more dramatic in its onset.

The patient was a man of 60 who had had a discharging left ear in childhood resulting in considerable deafness of that ear, although there had been no recurrence of the discharge. Two years before admission he had been aware of occasional spasms in the muscles around the left eye, and a year before admission he began to have attacks of gross spasmodic contraction of the left facial musculature: he described the platysma as "working up and down like a piston", and at times the whole of the left side of his face was contorted by irregular jerking movements. These were probably coarse fibrillations, but his description was so vivid that the question of focal epileptic attacks had to be considered. The facial weakness meantime was progressive, and about three months before admission, one of these spasms resulted in a complete left facial palsy, at least nine months after the onset of symptoms.

ON EXAMINATION.—He was a healthy man with a complete facial palsy on the left side (*Fig.* 32). He was very deaf in the left ear: with a noise box in the right ear, he could hear only loud shouts with the left ear. Weber was referred to the left. A.C. > B.C. right. B.C. > A.C. left. Both ear drums were somewhat dull, but otherwise normal. The caloric responses were absent on the left side but were present on the right. There were no other neurological abnormalities, and the spinal fluid was normal. Radiographs (*Fig.* 33) revealed an area of erosion of the petrous bone similar to that seen in the first case. The diagnosis was in no doubt in this case, and at operation on May 21, 1942, a lesion very similar to that in the first case was found. The facial nerve was identified in the cavity and it was intact although flattened. The wound healed normally, and he was discharged at the end of ten days.

By December, 1942, there was definite evidence of recovery, and this has continued until now he is able to close his eyes and to innervate the whole of the left side of his face (*Fig.* 34). It is interesting that his face now shows the phenomenon of mass innervation, i.e., he is not able to innervate one part without the whole. Thus, when he is asked to show his teeth, the orbicularis oculi contracts as well; and when he is asked to close his eyes firmly, the angle of his mouth moves. This phenomenon is well known in recovery from other types of facial paralysis, and it occurs in recovery from peripheral nerve lesions in other parts of the body.

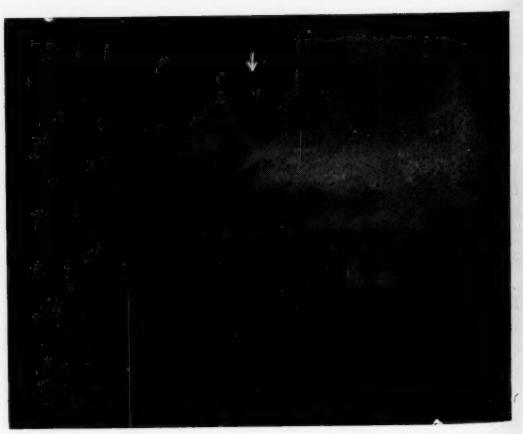
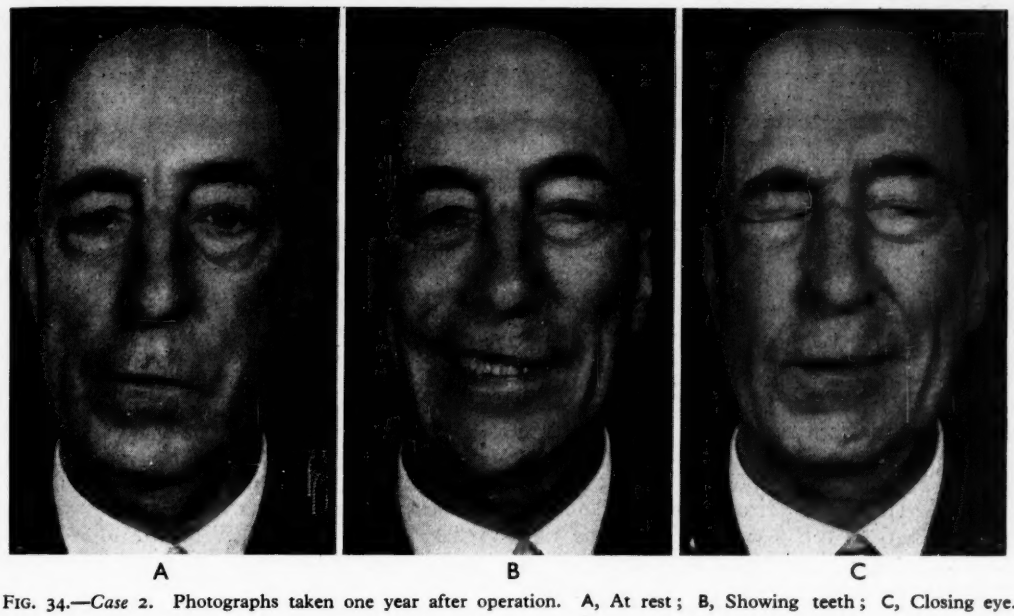


FIG. 33.—*Case* 2. Lateral projection of left petrous bone, showing erosion of superior surface.

Case 3.—This case calls for no special mention: it was that of a man of 53 who had had a facial palsy for four years. It came on so gradually that he could not say how long it took to become complete, but it had probably been so for at least two years before admission. He had had an attack of suppurative otitis media on the left side twenty-five years before, but, after discharging for about two weeks, this infection cleared up and he had had no further trouble with his ear. On admission there was a complete facial palsy on the left side, impairment of taste on the left side of the tongue, gross middle-ear deafness on the left side, a large dry perforation of the left drum, and absent caloric responses on the left side.



A B C

FIG. 34.—*Case* 2. Photographs taken one year after operation. A, At rest; B, Showing teeth; C, Closing eye.

Left *Right*

FIG. 35.—*Case* 3. Radiograph showing erosion of superior surface of left petrous bone.

The spinal fluid was normal, and radiographs (*Fig.* 35) showed an erosion of the petrous bone similar to that described above. At operation on March 22, 1943, a similar lesion to those in the first two cases was found. The wound healed normally and he was discharged in ten days. It is unlikely that any recovery will occur in this case, as although the galvanic reaction was present when he was seen as an out-patient, it was uncertain when tested immediately before operation.

DISCUSSION

These cases present many common features. They all had a peripheral facial palsy of gradual onset. In two of them there had been infection of the middle ear many years previously—in one twenty-five years and in the other about forty-five years—with no subsequent history of ear trouble. In the third case, the first evidence of aural infection of which the patient was aware occurred several months after the onset of the facial paralysis. In each case there was deafness of the homolateral ear, of a predominantly middle-ear type, and in each of them the deafness was more marked than one would have expected from the trivial nature of the aural infection. The caloric responses were absent. The sense of taste was impaired or lost in all cases. The neurological examination otherwise was negative, and in particular there was no evidence of increased intracranial pressure, nor of any disorder of the ocular movements such as nystagmus, nor of any trigeminal impairment. In each case the spinal fluid was normal. Radiographs of the skull showed an area of erosion in the petrous bone which was obvious in the routine axial views. The pathological findings at operation were similar in the three cases. There was erosion of the upper surface of the petrous bone by a soft, flaky white mass, creating a cavity in which the facial canal was bared between the internal acoustic meatus and the genu, and the nerve was subjected to compression. This soft white material had the naked-eye characters of a cholesteatoma, of the sort seen within the dura and bone elsewhere. Histologically it is laminated eosinophil material, for the most part devoid of any cellular elements. It was sterile on culture and the petrous bone and middle ears have shown

no naked-eye appearance of active infection, although, as mentioned in one case, there was some chronic inflammatory infiltration and thinning of the periosteum in fragments of bone removed from the margins of the cavity.

Jefferson and Smalley (1938) reported 6 of these cases in 1938 and found references to 5 others in the literature of the previous twenty-five years. They held that these tumours are probably epidermoids of the embryonal inclusion type rather than the cholesteatoma often associated with chronic mastoid infections. Their reasons for this view were that in at least two of their cases there had never been any aural infection, and in the others the infection was remote in time and trivial in degree. They considered that the common site of these tumours was an unusual one to be related to mastoid disease, being in a part of the petrous bone where there are normally no air cells. They raised again the question of primary cause: does a congenital tumour which we call a cholesteatoma cause infection of the middle ear and mastoid, or is the cholesteatoma the product of chronic inflammation. This is a controversy which is not likely to be settled at once, but in favour of a primary infection it can be said that in 6 of the 9 cases (taking the two series together) there had been antecedent mastoid disease in the same side, and that the possibility of such an infection having been unnoticed or forgotten in the other cases cannot be excluded. We know, for instance, that occasionally a temporal-lobe abscess can result from an acute infection of the middle ear and mastoid which resolves completely and leaves no signs.

For practical purposes, the aetiology of these tumours is less important than their recognition clinically. Although they are benign lesions, if they are treated in time recovery may take place, as in one of the cases described above, and in one of Jefferson and Smalley's series.

The operative approach which we have used is similar to that for the middle-fossa division of the sensory root. Jefferson and Smalley approached them through the mastoid, but as in each of our cases the erosion was in the superior surface of the petrous bone, it was easily accessible from above. Careful X-ray studies would show which route was preferable, and a combined approach might be of value in some cases.

The operation should be done as soon as the diagnosis is made, and the same factors will influence recovery as operate in other cases of facial palsy. The best chance of complete recovery rests in operation before the paralysis is complete or as soon thereafter as possible. Electrical treatment should be continued after operation until recovery is certain, or until it is clear that no improvement can be expected, in which case other methods of re-innervation will have to be employed.

The differential diagnosis from cerebello-pontine angle tumours has already been mentioned. Enough has been said to show that that differentiation is not difficult. What is more difficult is saying whether or not these are Bell's palsies, and that, in fact, is what all of our cases were first thought to be. The mode of onset and the X-ray changes should leave the matter in no doubt if the possibility of this lesion is borne in mind. It is probably not as uncommon as the literature would suggest: a careful study of any large series of facial palsies would probably reveal several examples.

The ultimate potentialities of these tumours are uncertain. If they develop from embryonal rests which wait until middle life to produce symptoms, they must be very slowly growing, and apart from local destruction of the internal ear and facial nerves, they might allow a normal span of life without any further disability. It is possible that the tumour might erode the dura of the middle cranial fossa and invade the brain, but such an occurrence has not been described in any of the published cases.

SUMMARY

1. Three cases of facial palsy due to cholesteatoma of the petrous bone are described.

2. The differential diagnosis from other causes of facial palsy is discussed.

3. It is suggested that the best chance of recovery in these cases rests in early operation and subsequent electrical treatment.

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JEFFERSON, G., and SMALLEY, A. A. (1938), "Progressive Facial Palsy Produced by Intratemporal Epidermoids", *J. Laryng.*, **53**, 717.

ADRENAL NEUROBLASTOMA

BY T. A. OGILVIE

NEUROBLASTOMA occur almost entirely in infants and young children. The number of cases reported in the literature is approximately three hundred, and the experience of any one surgeon cannot include many examples of the disease. The diagnosis, as in the case reported here, may present difficulties both from the clinical and histological aspects, and it is likely that many cases are only diagnosed late, when metastases are widespread, or at post-mortem examinations. With few exceptions, treatment has so far been quite ineffective, and if improvement is to occur, early diagnosis is essential as in other malignant conditions.

CASE REPORT

E. W., female, aged 2 years 10 months, was admitted to hospital on May 8, 1941, with a history that for six months there had been a gradually increasing swelling of the abdomen. There was no lassitude, sickness, or pain, and the child otherwise appeared well. Micturition was normal, and bowels were regular.

On Examination.—There was a tremendous enlargement of the abdomen, the girth of which was 27½ in. A firm, smooth, non-fluctuant mass filled most of the abdominal cavity, extending from the right costal margin down to the pelvis and well over to the left side. The veins of the abdominal wall were greatly distended (*Fig.* 36).

A plain radiograph of the abdomen showed that the diaphragm was raised on the right side. A large homogenous soft-tissue shadow filled the whole right abdomen and extended over to the left, the colon shadow being displaced to the left. An intravenous pyelogram showed a functioning left kidney; no dye appeared in the right kidney.

Blood-urea, 27 mg. per 100 c.c.
Blood-pressure, 115/47.
Blood-count :—

Erythrocytes	4,600,000	
Leucocytes	8,700	
Polynuclear neutrophils	32	per cent
Polynuclear eosinophils	3	,, ,,
Small lymphocytes	27	,, ,,
Large lymphocytes	29	,, ,,
Large hyalines	7	,, ,,

Hæmoglobin, 73 per cent

At Operation.—Owing to an attack of scarlet fever, laparotomy was not performed until June 10. A very large moveable retroperitoneal tumour was displayed, with many engorged veins coursing over the surface. The tumour was not adherent except in the region of the right renal pedicle, and was removed together with the compressed kidney. The tumour weighed 7 lb. 12 oz. (*Figs.* 37, 38).

Progress.—Convalescence was uneventful and the child was discharged from hospital on July 26. A course of deep X-ray therapy was subsequently given at the Middlesex Hospital. She was readmitted on Dec. 22 with one month's history of pains in the back and difficulty in walking. A tumour was present over the superior and lateral aspect of the left orbit, and there was marked proptosis of the eye (*Fig.* 39). Paresis of the lower limbs was evident.

Fig. 36.—Photograph before operation, showing distended abdomen and dilated veins.

The patient slowly and gradually went downhill, the proptosis increased, the lower limbs became completely paralysed, incontinence of urine and fæces was present, and she died on April 26, 1942.

At Autopsy.—The post-mortem examination showed that the left orbit was filled with new growth which protruded into the cranial cavity. The brain was not invaded. A mass of new growth was seen in the region of the sixth and seventh dorsal vertebræ, and this had invaded the neural canal, compressing the cord. A recurrence, the size of a man's fist, was present at the site of the right kidney. A few secondaries were present in the diaphragm and in the liver.

Fig. 37.—Photograph of the neuroblastoma.

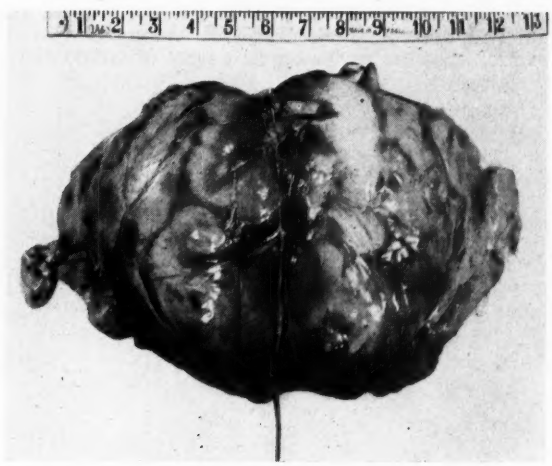


Fig. 38.—Photograph showing a probe in the ureter.

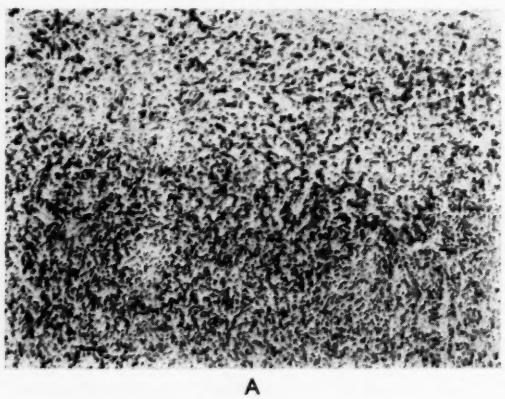
Histology.—The histological reports were of great interest. Dr. J. R. Gilmour, to whom I am greatly indebted for several communications, reported: "Portions of spindle- and polygonal-celled diffuse sarcoma from kidney; no epithelial or teratomatous tissue present. The appearance of the sarcoma is similar to that usually present in a teratoblastoma of the kidney, but in the absence of differentiation into

epithelium, and of muscle, the tumour cannot be regarded as a teratoblastoma or Wilm's tumour."

A later note stated that the cells were: "Polymorphic—stellate, flat, and spheroidal, variable density of cells with some areas poor in cells and rich in collagen; tendency to form ill-defined spaces". He was of the opinion that the tumour was not a neuroblastoma.

FIG. 39.—Showing the orbital metastases and the proptosis of the eye.

Dr. H. A. Lucas also kindly examined the sections and reported: "The neoplasm is composed of cells which show only a moderate degree of differentiation. They are not the round primitive type. Rosettes are present, stroma is very scanty, blood-vessels are chiefly of the small capillary type. A few cells show some resemblance to ganglion cells. The presence of nerve-fibrils is suggested in several areas, but were not clearly demonstrated in the stained sections examined. The neoplasm in my opinion arises from the developing sympathetic system in the medulla of the suprarenal, and is probably of neuro-epithelial origin, the cells showing a slightly greater degree of differentiation than is present in some of the clinical types recorded. These neoplasms have been described under various names, neurocytoma seems to be the most appropriate."



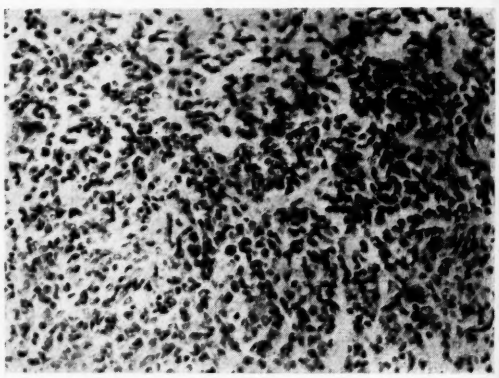
A

FIG. 40.—Microphotographs showing arrangement of cells. A, × 60; B, × 150; C, × 150.

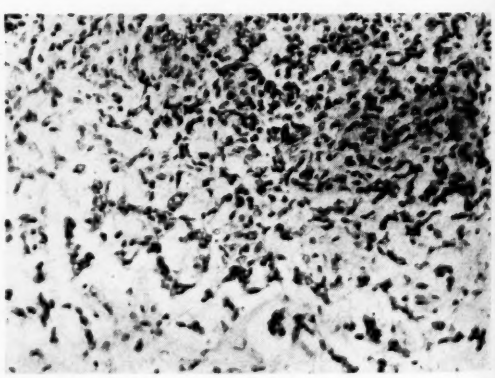
Unfortunately, it was not possible to have the sections specially stained for neuro-fibrils.

DISCUSSION

In the above case, and in many previously reported, some doubt has remained as to the correctness of the diagnosis, and an explanation may lie in the fact that various types of tumour arise from the adrenal gland. This can be shown by reference to the development of the gland. The adrenal cortex is of mesodermal origin and first appears in the early embryo as a ridge close to the Wollfian body. The cortex has an influence on the secondary sex characteristics, and in tumours of the cortex these are frequently profoundly altered. The medullary cells, on the other hand, arise from the ectoderm of the primitive neural crest, and during the early growth of the embryo they become widely distributed throughout the sympathetic system, where they develop into sympathetic ganglia, Schwann cells, and chromaffin tissue. These primitive cells are rarely seen after the first few



B



C

weeks of intra-uterine life, but may be found in the adrenal medulla throughout fœtal life, and may occasionally persist after birth. The fact that these cells undergo differentiation later than the other cells of the central nervous system may be a contributing factor in the frequent localization of tumours composed of primitive nerve-cells in the adrenal medulla. According to Potter (1942), sympathetic nerve-cells at the time of their migration from the neural crest are histologically similar to those of the central nervous system. They are small cells with hyperchromatic nuclei and scanty protoplasm, and tumours composed of such cells are neuroblastomas, or, more accurately, sympathogoniomas. In the normal process of development, the cells grow larger slightly vesicular nuclei and the cytoplasm increases in amount. The cells are now known as sympathicoblasts and tumours as sympathicoblastomas. The term 'neuroblastoma', as usually used, includes both types of tumours. In further development, the sympathicoblasts mature into chromaffin cells, ganglion cells, and Schwann cells, and tumours composed of these cells are known as pheochromocytomas, ganglioneuromas, and neurofibromas respectively. These tumours may all show a variegated picture owing to the different degrees of differentiation and to the varying relative proportions of cells and fibres which are present.

The neuroblastoma is therefore a highly malignant tumour of the sympathetic nervous system, being derived from the undifferentiated neuroblast. It may occur wherever the neuroblast is present, and is most common in the adrenal medulla, less frequent in the sympathetic ganglia, and, contrary to what one might expect, rare in the central nervous system.

The primary tumour is a soft nodular growth, usually well encapsulated, and shows a considerable variation in size. Growths as small as 1 cm. are reported as well as are large bulky tumours filling the greater part of the abdominal cavity. As the primary growth remains encapsulated, it does not usually spread to neighbouring organs, with the exception of the liver, which is invaded by direct spread through the bare area. The kidney is usually indented and compressed, but not often invaded. It might be expected that the tumour would destroy or compress the adrenal cortex, with the production of changes in the secondary sex characteristics, but, according to Broster et al. (1938), this is extremely rare. Smith (1932), however, reports a case which showed evidence of hirsutism and marked overgrowth of the eyelashes.

The primary growth is very liable to hæmorrhage and degeneration, which alters the original yellowish-grey colour of the tumour. Microscopically, it is composed of small round or oval cells with nuclei that resemble lymphocytes, and with very little cytoplasm. Interspersed between groups of the cells are ill-defined fibres which have been identified by special staining reactions as axis cylinder processes and neuroglial fibres. Wright (1910) first described these fibrils, which tend to form longitudinal bundles or round masses surrounded by groups of neuroblasts forming the so-called rosettes. This rosette formation is found in one-third to one-half of the cases reported.

The neuroblastoma has a close resemblance to a round-celled sarcoma, and it is probable that many cases have been overlooked. Ewing states that it is necessary to include in this group most of the retroperitoneal round-celled sarcomas of infants, and many similar growths of the cervical, thoracic, and peripheral nervous systems.

Since the time of Pepper (1901) and Hutchison (1907), neuroblastomata have been classified into two clinical types, but it is now well known that there is an irregular type, and that the above classification does not always hold good. Wright's histological studies showed that the Pepper and Hutchison syndromes are just different manifestations of the same disease. The Pepper type is characterized by abdominal symptoms resulting from the primary growth and the metastases to the liver, while the Hutchison type is characterized by its distant metastases to the cranial bones. Frew (1911) endeavoured to explain this difference in the route and appearance of the secondary growths on the basis of the different lymph drainage of the two adrenal glands. The lymphatic vessels from the left adrenal communicate with the aortic chain of lymph-glands and cells from a left-sided growth may reach the thoracic duct and the cervical lymph-vessels and thence to the skull. The right adrenal is in direct contact with the bare area of the liver, to which the growth may spread by contiguity, while lymphatic paths along the inferior vena cava may carry the tumour to the pleura and lungs, which are not usually affected by left-sided growths. Frew's theory has not been found correct, and a review of the literature shows that the side on which the primary growth arises has little to do with the distribution of the metastases. In 56 Pepper-type cases, the primary growth was situated in the right gland in 27, in the left in 21, and in both in 8 cases. In 83 Hutchison-type cases, the primary growth was situated in the left gland in 38, in the right in 35, and in both in 10 cases. The Pepper type runs a more rapid course than the Hutchison type, indicating a more cellular growth and more rapid dissemination. As Chont (1941) points out, in all types of tumour, rapid and slowly-growing varieties occur, and metastases are seen long after cure at the primary site, indicating that these secondary growths remaind dormant for some considerable time.

Neuroblastomas, therefore, probably give rise to distant metastases at a relatively early stage of their growth. In the rapidly growing Pepper type these distant metastases remain small, and death occurs before they reach such a size as to

influence the clinical picture. In the more slowly growing Hutchison type the distant metastases form one of the striking features of the disease. The clinical type, therefore, to which a case conforms may depend more on the rate of growth of the primary tumour than the side of the body in which it arises.

CLINICAL FEATURES

Neuroblastoma is a disease of young children, but there are several recorded cases occurring in adults: Ballard (1940) reported 1 case in a man of 69, and Weichselbaum 1 in a man of 72. It is undoubtedly a rare condition, and Law (1932) reports that at the Paddington Green Children's Hospital only 4 cases occurred in twenty years, and at the Hospital for Sick Children, Great Ormond Street, only 6 cases occurred in six years. Tumours arising from organs other than the adrenal are still more rare. According to Boyd retinal tumours show a striking familial tendency, and there is a case on record where in a family of sixteen, ten children died of the disease.

While it is clinically convenient to retain the classical Pepper and Hutchison types, it must be recognized that this division is arbitrary, and that cases occur which cannot be placed in either group.

The Pepper type occurs in young children usually under 2 years, is of short duration, and terminates fatally in a few months. The characteristic feature is great distension of the abdomen, due partly to the primary growth, but mainly to the enormous enlargement of the liver which results from invasion by the malignant cells. Nausea and vomiting may occur, but ascites is not, as a rule, present.

The Hutchison type is seen in slightly older children, usually over 2 years of age, and runs a longer course. Frequently it is only recognized after the occurrence of metastases, which are usually seen first in the region of the orbit and skull and later in the vertebral column or long bones. While the primary growth may form a large tumour weighing several pounds, it frequently is very small and is only discovered at post-mortem examination. The most striking feature is the proptosis of one or both eyes due to the intra-orbital metastases, and in advanced cases the eye may be almost dislocated from the socket. Swelling and ecchymosis of the eyelids usually precede the proptosis. Movements of the eyeball, vision, and the pupil reflexes may be impaired, but not necessarily so, and papillœdema is present in advanced cases. Ulceration of the cornea may occur as a result of the eyelids being unable to close over the proptosed eye. Owing to the increased intracranial pressure, separation of the cranial sutures may occur, the coronal suture being most often affected.

In both clinical types the above features are accompanied in the later stages by pallor, wasting, and listlessness, and an irregular temperature is common. Anæmia is very common, particularly in advanced cases of the Hutchison type. Painful swollen joints may simulate rheumatic fever, and tenderness over the metaphysial ends of the long bones may result from bone metastases. A leucocytosis may occur, but is not of marked degree. Both Law (1932) and Smith (1932) report the presence of subcutaneous nodules over the chest wall, anterior abdominal wall, and forearms, but these are distinctly rare and have not been reported by other observers.

DIFFERENTIAL DIAGNOSIS

Neuroblastomas have to be distinguished from Wilms' tumours, and errors in diagnosis are more likely to occur in the irregular types of cases. The case here reported was thought to be a Wilms' embryoma prior to operation, but the subsequent progress led to the alteration in the diagnosis. Wilms' tumour usually occurs in children under 2; hæmaturia may occur, but by no means invariably. Bone metastases in Wilm's tumour are rare, but when they occur the pelvis is the most frequent site.

Ewing's sarcoma may also be a common source of error. Willis (1940) draws attention to the fact that the skeletal metastases in neuroblastoma may present all the clinical features of a Ewing's sarcoma. He describes two such cases and comes to the conclusion that the subject of Ewing's sarcoma is chaotic, that the occurrence of a primary growth of this nature is still unproved, and that metastatic growths of various types, particularly neuroblastoma, may be responsible for many of the cases of Ewing's sarcoma.

Tumours of the adrenal cortex are characterized by the changes in the secondary sex characteristics, and frequently by elevation of blood-pressure.

The osseous changes in leukæmia may closely resemble those of neuroblastoma, but repeated blood studies and sternal punctures will lead to the correct diagnosis.

In American literature, Chont (1941) and Wyatt and Farber (1941) have recently described the radiological appearances in a series of cases. There is no characteristic radiological picture, but in a small number of cases calcification has been seen in the primary tumour. The calcium deposits vary from fine uniform stippling to irregular confluent shading throughout the tumour mass. A pyelogram is no real aid to diagnosis, and its main function is to demonstrate the presence of the opposite kidney. It is impossible to tell whether the tumour arises within the kidney or from the adrenal, but it may show downward displacement of the kidney and ureter.

In cases with cranial metastases, the skull bones may show innumerable areas of destruction varying in size from pin-point to several millimetres in diameter. In some cases round areas of destruction are seen indistinguishable from

secondary carcinoma or sarcoma. The metastases to long bones are more characteristic and the striking feature is the frequency of bilateral symmetrical lesions. In the majority of cases, bone destruction and proliferation are seen in the form of small discrete lesions or confluent areas of destruction with a small amount of proliferation of surrounding bone. Massive destruction is usually seen at the metaphysis and pathological fracture may occur.

TREATMENT

Treatment so far has proved extremely disappointing, and a fatal issue can be expected in one to ten months from the onset of symptoms. Extremely divergent views on treatment have been expressed, and some writers believe that surgery is harmful and radiotherapy not beneficial. Lehman (1932), however, reports a case alive and well fifteen years after operation, and, more recently, the response to radiotherapy has been such as to provide encouragement for further efforts in this direction. While the fatal issue has not been averted by radiotherapy, temporary disappearance of secondary deposits has been reported. Willis's case, thought to be a Ewing's sarcoma, was proved to be highly radiosensitive, and was effectively controlled by radiotherapy for over two years. The method of choice, therefore, would appear to be surgical removal of the primary tumour, with subsequent irradiation of the area involved.

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LOCAL SULPHANILAMIDE TREATMENT OF FRESH WOUNDS IN COMPLETE PLASTERS

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THIS investigation aimed at obtaining incontrovertible evidence about the effect of local sulphanilamide on the bacteriological condition of compound fractures and other severe wounds treated by thorough cleaning and excision, followed by enclosure in plaster; and at correlating this with the clinical results.

Frequent and complete observations were made on 32 patients, of whom 18 received local sulphanilamide and 14 did not. None had general chemotherapeutic treatment.

At first all cases were sulphanilamide-treated, as we believed we had a satisfactory control series, not so treated, which had been investigated in the previous year; but after a time we realized the unsoundness of the principle, as experience and organization had steadily improved the surgical results apart from sulphanilamide treatment. In the latter part, therefore, we treated contemporary series of cases with and without local sulphanilamide, attempting to avoid any 'selection' that might vitiate our conclusions. This attempt was, on the whole, successful. Although the two groups could not be absolutely uniform in severity and delay before treatment, the balance in both respects is weighted against the sulphanilamide group. In the latter, the interval between wounding and operation ranged from 2½ hours to 10 hours; in the 'untreated' controls from 1 hour to 5½ hours, the average being 5 hours in the former and 4 hours in the latter. The 'treated' group, moreover, contains a rather larger proportion of gravely injured patients. The complete sulphanilamide series includes the 10 cases which were sulphanilamide treated in the previous year, without strictly contemporary controls. Any subsequent deterioration of clinical treatment would have invalidated the comparison, but we are certain that no such change occurred. Nevertheless, the smaller,

fully controlled series, excluding the 10 cases, has been separately analysed, and shows a significant bacteriological superiority of the sulphanilamide group in the second week, when the scanty bacteria left after the operation have had full time to develop.

Bacteriological examinations were made by cultivating all tissue excised at the primary operation, by taking swabs at changes of plaster, and at other times by swabbing through special 'windows'. Direct microscopical examination of films from the swabs gave us a rough estimate of the degree and nature of the bacterial contamination, and of the cellular exudate. Complete bacteriological analyses were made each time as described in the *British Medical Journal*, (1941, 1, 877), with certain additions, such as para-aminobenzoic acid blood-agar. The amount of bacterial growth on direct platings was noted, and this, combined with density of the bacterial population in the films, is expressed in *Table I* by the number of plus signs. Statistical analysis shows that the total bacteria in the sulphanilamide-treated wounds are significantly less than in the controls during the first 14 days after a single application of the drug. After 14 days the difference is not significant.

Regarding individual bacterial species: Hæmolytic streptococci were found in 6 sulphanilamide-treated wounds at the operation, and 5 of these disappeared as the result of operation and sulphanilamide treatment, while 1 persisted. Of the control wounds, 4 showed this organism at the outset, and in all 4 it persisted throughout the period of observation.

Staphylococcus aureus was found in 23 out of the 32 wounds. Its numbers were lower in the sulphanilamide-treated wounds, but the frequency with which it disappeared after sulphanilamide was only slightly greater than in the controls. In the great majority of both series it persisted throughout. Anaerobes were scarce and unimportant; the few *Cl. welchii* present in excised tissues failed to reappear in both series. Gram-negative rods, proteus, *Ps. pyocyanea*, etc., were unaffected. Assessment of the amount of inflammatory exudate from the macroscopical and microscopical examination of the swabs, though more difficult than that of the bacteria, showed a statistically significant reduction in the sulphanilamide series in the second week (during the first week there was hardly any in either group).

The clinical results in both series were uniformly good, and no evidence was obtained that the local sulphanilamide affected the clinical progress of the cases.

Thus we have demonstrated a selective reduction of the wound flora by sulphanilamide, but we have not established a corresponding clinical effect.

(Full details of the work, of which this article is a résumé, with discussion and references, may be obtained from the Medical Research Council, to whom we are indebted for financial support. Our thanks are also due to Mr. P. H. Leslie and Professor M. Greenwood for statistical help.)

Table I.—NUMBER OF WOUNDS SHOWING HIGH OR LOW DENSITY OF TOTAL BACTERIA AT DIFFERENT TIMES

	Complete Series								Strictly Contemporary Series			
Density of Flora	Days 3–7		Days 8–14		Days 15 to Plaster-change		Second Plaster Days 1–20		Days 3–7		Days 8–14	
	S	C	S	C	S	C	S	C	S	C	S	C
Low (o to +)	14	5	13	1	7	2	3	0	6	5	6	1
High (++ to ++++)	2	8	3	11	6	8	2	6	2	8	2	11
χ_c^2	5·618		11·812		1·483		2·387		1·388		6·676	
P (n = 1)	<0·02 >0·01		<0·001		<0·3 >0·2		<0·2 >0·1		<0·3 >0·2		<0·01	
Statistical conclusion	Significant		Significant		Not significant		Not significant		Not significant		Significant	

S, Sulphanilamide; C, Control (no sulphanilamide).
Note: Not all the wounds in each series were observed at every period.

MINIATURE SCAR-CARCINOMA OF THE LUNG AND THE "UPPER SULCUS TUMOUR" OF PANCOAST

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In recent years considerable attention has been focused on a group of tumours arising in the neighbourhood of the apex of the lung. Pancoast (1924, 1932) suggested for this group the term 'superior pulmonary sulcus tumour', because they presented certain features which differentiated them from other tumours in this region: (*a*) The tumours were localized in the superior thoracic inlet; (*b*) They were malignant and the histological picture was that of a squamous-celled carcinoma; (*c*) They produced symptoms and signs by invasion of neighbouring structures—the brachial plexus, causing pain referred to the upper limb, with wasting of the muscles, and the sympathetic, producing a Horner's syndrome on the affected side; (*d*) The tumours are independent of the lung and pleura and other structures in the neighbourhood, and there is no evidence of a primary focus elsewhere. For this reason Pancoast suggested an origin from branchial rests.

The clinical features of this group are certainly well defined, but the site of origin is still a matter for discussion. For this reason the details of two cases recently under our care are presented. Although the clinical picture of spinal cord compression was unusual, the other features were characteristic. The investigations appear to throw light on some of the controversial points associated with this group of neoplasms.

CASE REPORTS

Case 1.—G. S., a man aged 60, had complained of intermittent pain between the upper part of the shoulder-blades for thirteen months. This had become more intense during the five months preceding admission to hospital, but he was able to work until five weeks before, when the pain became too severe. Three weeks before admission his legs began to get weak, and within three days he was unable to walk. During this period he had noticed 'pins and needles' in his legs. For a week before admission he could not pass urine and was catheterized twice daily. He had been incontinent of fæces. During the last month he had lost weight and had become short of breath.

On Examination.—There was a moderate amount of wasting, a flaccid paraplegia, and a complete sensory loss up to the level of the third thoracic segment. A Horner's syndrome was present on the right side. No other abnormality could be found in a careful general examination. Radiographs of the chest revealed an opacity of small size in the superior mediastinum to the right of the first and second dorsal vertebræ, but radiographs of the spine showed no involvement of the bodies of the vertebræ, the intervertebral foramina, or the ribs. Lumbar puncture yielded clear, colourless cerebrospinal fluid at a pressure of 160 mm. Pressure on the jugular veins showed an incomplete block. The fluid contained 2 lymphocytes per c.mm., and 500 mg. of protein. The Wassermann reaction was negative. Cisternal injection of lipiodol showed a complete block at the level of the first thoracic vertebra.

At Operation.—Laminectomy of the upper thoracic vertebræ revealed a firm, pinkish, extradural tumour 'en plaque' surrounding the dura mater at the level of the second and third thoracic vertebræ. The tumour was closely adherent to the dura. The latter was opened and was found to be thickened in places to nearly $\frac{1}{4}$ in. by tumour tissue. The cord at the level of the first thoracic vertebra was dumb-bell-shaped from compression. No intradural extension was found. A frozen section was made and this revealed a squamous-celled carcinoma with frank prickle cells embedded in much fibrous stroma. Tumour tissue was removed to free the cord and the dura was left open. Closure of the wound was made in layers.

Fig. 41.—*Case* 1. Apex of the right lung with pleural cap (arrow) and emphysematous bullæ in the subapical lung tissue.

He was not improved by the operation, and died one month later from bronchopneumonia and pyelonephritis.

AT AUTOPSY (P.M., 1943/167).—The right apex was found adherent to the pleural dome; it was, however, easily separated without loss of substance (*Fig.* 41). The apex of the lung showed a typical

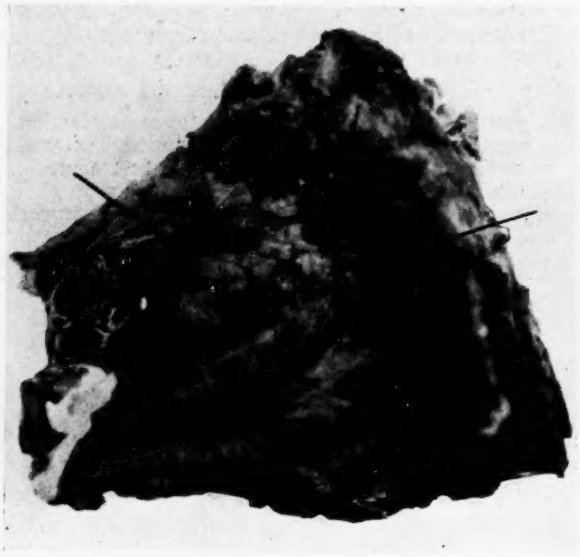

FIG. 42.—*Case* 1. Flat subpleural nodules (arrows) in the right pleural dome.

'pleural cap', with a little induration but no gross, naked-eye evidence of a neoplasm. In the pleural dome on its inner aspect, however, there was a growth consisting of two flat subpleural nodules, measuring together 3 × 3 cm. in diameter (*Fig.* 42), fixed to the inner ends of the second and third ribs, and extending by continuity into the body of the second and third thoracic vertebræ, the former being compressed into a wedge. In this region the tumour had infiltrated the dura mater of the cord constricting it, without, however, involving the substance of the cord. Meticulous dissection of the whole bronchial system and careful examination of the extrapulmonary organs, including pharynx, œsophagus, brain, bones, and suprarenals, failed to reveal any evidence of growth, primary or metastatic. Death was due to necrotizing cystitis and pyelitis with multiple abscess formation in both kidneys.

HISTOLOGICAL EXAMINATION.—

The *growth in the right pleural dome* exhibited the same structure as that seen in the biopsy sections. There were strands and sheets of squamous and prickle cells and also alveoli with horn pearls in the centre. In some areas stroma was abundant, in others scarce.

The *apex of the left lung* which had been slightly adherent to the growth was examined in a complete series of sections. It consisted of:—

a. A typical, hard, fibrotic, almost structureless pleural cap, devoid of elastic fibres (*Fig.* 43, C).

b. A circular band of fibrotic apical lung tissue containing many curly elastic fibres, obviously the remnants of collapsed and compressed lung alveoli (*Fig.* 43, B).

The pleural cap and the fibrotic apical tissue were clearly separated by the thickened, deep elastic membrane of the pleura.

c. Between the pleural cap and the circular band of fibrotic and elastic tissue an almost homogeneous scarred area with much anthracotic pigment was found. It was about 3 × 3 mm. in size. In its centre (*Fig.* 43, M) there were a moderate number of distended alveolar spaces, some of them with elastic septa.

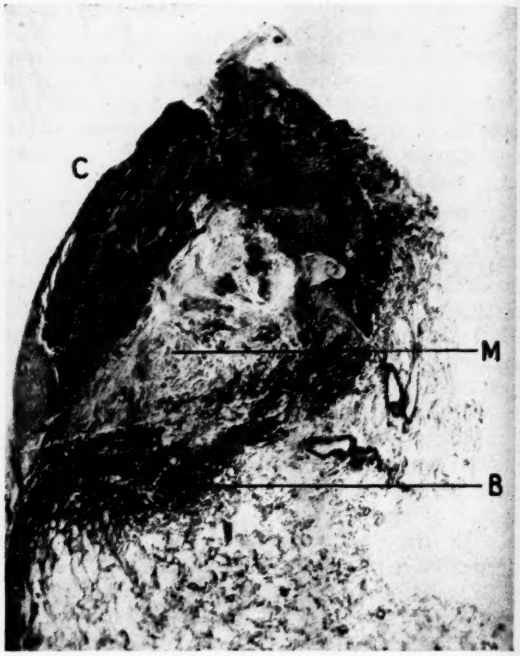

FIG. 43.—*Case* 1. Survey of histological section through right apex. C, Pleural cap; M, Focus of miniature carcinoma with 'sebaceous' material in distended alveolar spaces; B, Circular band of fibrotic elastic lung tissues. Weigert's stain for elastic fibres; counterstained with safranin. (× 6·6.)

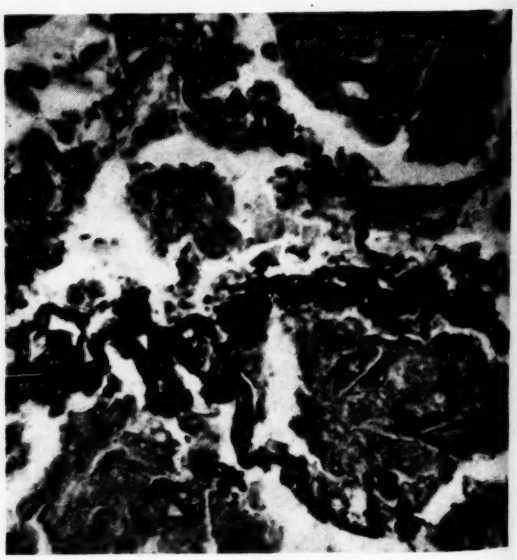

FIG. 44.—*Case* 1. Miniature carcinoma. Distended alveoli filled with flat 'horny' cells. Weigert's elastic stain. (× 165.)

These spaces were filled with 'sebaceous' material, i.e., desquamated, flat, 'horny' cells, some with, others without, nuclear remnants (*Fig.* 44). Some of these sebaceous plugs were surrounded by seams of

squamous or prickle cells (*Fig.* 45). There were also a few horn pearls. Towards the periphery of this area the 'sebaceous' material was seen to disappear gradually. On both sides some slender, compressed-looking strands of prickle cells, and in the marginal areas larger units of such elements, emerged (*Fig.* 46).

Comment.—Meticulous post-mortem examination of the bronchial tree, the lungs, and extrapulmonary organs failed to detect a growth primary to the tumour in the pleural dome. This was a prickle-celled (squamous-celled) carcinoma with hornification. It was marked out by its tendency to invade the bony structures of the inlet of the chest. It had caused a 'Pancoast' syndrome—although this was complicated by the signs of spinal-cord compression. Thus a genuine instance of 'tumour of Pancoast' seemed to lie before us.

Serial sectioning of the lung apex, however, revealed between a thick 'pleural cap' and a circular band of compressed and thickened lung tissue the presence of tumour-cell units situated in an anthracotic scar. Its centre was occupied by alveoli with elastic septa containing 'sebaceous' material surrounded by bands and strands of squamous cells. On both sides, towards the periphery, these cellular units became more solid, and the 'sebaceous' alveoli disappeared. The origin of the tumour in the pleural dome and the problem of the 'Pancoast tumour' at large obviously rests with the interpretation of these findings in the apex of the lung. For this was certainly involved, although only detected microscopically. Three questions presented themselves: (1) What is the relationship between the apical scar and the cancer-cell units? (2) Can evidence be adduced of a secondary invasion of the apical lung tissue from the growth in the pleural dome? (3) Are similar changes in pulmonary scars known without growth in the pleural dome? In other words, could their interpretation as a lesion antedating that in the pleural dome be justified?

FIG. 45.—*Case* 1. Miniature carcinoma. Sebaceous plug, surrounded by seam of squamous cells. Hæmatoxylin and eosin. (× 66.)

1. The pleural cap as well as the apical scar is identical in all histological detail with the ordinary indurative changes found so often in this region as a sequela to tuberculous infection or to the accumulation of dust. They far exceeded in extent and intensity the involvement of the area by carcinoma, and from the thickness and hyaline nature of the fibrous tissue the impression was derived that they antedated the growth. The presence of the apical scar is, therefore, no evidence against an extrapulmonary origin of the growth.

FIG. 46.—*Case* 1. Miniature carcinoma. Marginal parts. Units of prickle cells (P), with intercellular bridges. (× 135.)

2. If the growth was extrapulmonary in origin it must have invaded the dense tissue of the apical scar and found the way to its centre. Invasion of thick fibrous structures is possible, as shown by a few carcinomatous units seen in the outer marginal parts of the very dense fibrotic pleural cap. Against this interpretation, however, is the very central position of the 'sebaceous alveoli' in the apical scar. These show the most advanced horn production, i.e., conversion into sebaceous masses with only occasional preserved epithelial units. Deposition of sebaceous material was seen in these areas alone. We have, therefore, the most advanced hornification, i.e., the oldest changes in the centre of the apical scar, from which on both sides carcinomatous cell units radiate out towards the periphery.

3. Similar changes to those described independent of pleural or pulmonary carcinoma are known. They were placed on record under various headings, such as "Unusual proliferation of atypical and heterotopic epithelium in bronchiectasis" (Pagel, 1926, whose article should be consulted for further references), and "A microscopic focus of oat-cell carcinoma in a bronchiectatic lung" (Stewart and Allison, 1943), etc. These occur in pulmonary scars, notably those due to bronchiectasis. In other words, there exists a 'miniature carcinoma' which may either be detected accidentally, or may have formed the transitional stage between the metaplastic changes found commonly in bronchial epithelium of dilated bronchi and bronchial carcinoma. As a rule, these miniature carcinomata consist of a group of alveoli situated in dense fibrotic scar tissue and filled with oblong 'basal cells' which are rich in chromatin. In Pagel's observation there were, in addition, typical prickle

cells and cucumber-shaped masses of homogeneous material, giving all the histological appearances of hornification.

In the present case the oldest changes consisted, therefore, of a focus of epithelium with advanced hornification situated in the centre of an apical scar. Bronchiolar ectasis due to collapse induration and fibrotic shrinking of apical lung tissue led to metaplastic changes, i.e., the formation of squamous-cell nests and 'sebaceous' material. These may have been present for a long time and might have been discovered accidentally had death occurred from another disease at an earlier date. In this case, however, the sebaceous cell-nests had the chance to develop malignant properties. Their unusual situation may explain the unusual course: instead of invading the lung tissue below the dense fibrotic scar, they radiated out to the periphery between scar and pleural cap, and involved the pleural dome and by continuity the bony structures on the inner aspect of the pleural dome.

While the investigations of this case were fresh in our minds another case with a picture of spinal-cord compression presented itself. The clinical picture and the radiological evidence was so similar to the previous case that a diagnosis of the cause of compression could be confidently made.

Case 2.—J. N., a man aged 62, had complained of intermittent pain in the left side of the chest at the level of the third rib for about eleven months. This pain would shoot from the shoulder-blade to the front of the chest and down the inner side of the arm to the elbow. Although the pain gradually increased in severity, he was able to carry on with his work until he developed weakness of both legs six weeks

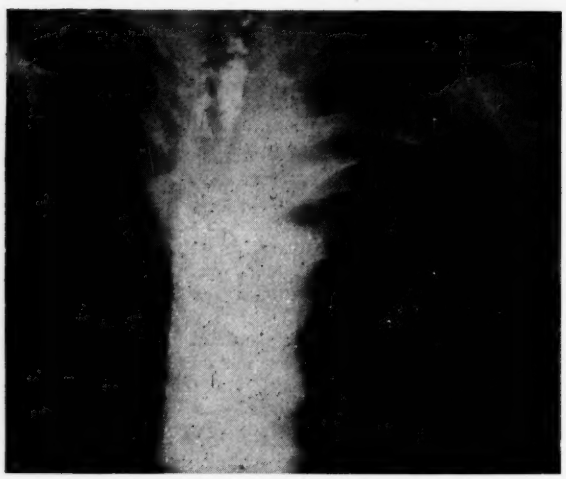

FIG. 47.—*Case* 2. Lipiodol block at the level of 3rd thoracic vertebra. Opacity to left of upper thoracic vertebræ.

before admission. Within three weeks he had lost the use of his legs completely. Two weeks before admission he could not pass urine and he had to be catheterized. His previous history was free from incident. There was no history of a cough.

ON EXAMINATION.—He was an emaciated man in poor general condition owing to infection from cystitis and pressure sores. He had a spastic paraplegia with flexor spasm and loss to all forms of sensation up to the level of the fourth thoracic segment. No Horner's syndrome was present. He was tender over the third thoracic spinous process. Radiograph of the chest revealed a small, oval opacity in the superior mediastinum to the left of the third

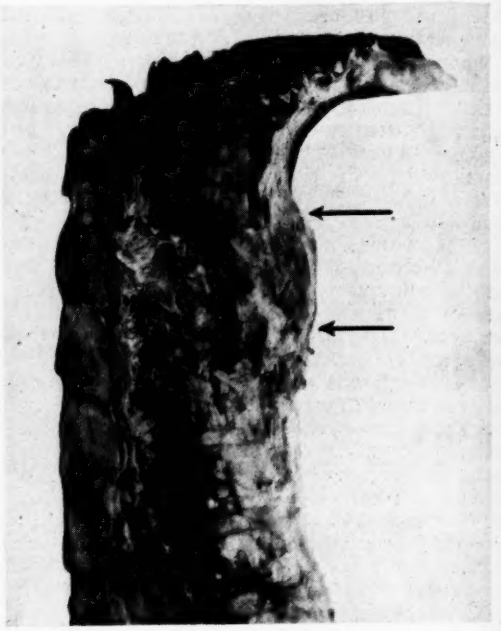

FIG. 48.—*Case* 2. Soft subpleural growth (arrows) in proximity to 3rd and 4th thoracic vertebræ.

thoracic vertebra (*Fig.* 47). Radiography of the spine showed pitting of the left transverse process of the third thoracic vertebra and a little irregularity in the left side of the body.

Lumbar puncture revealed clear cerebrospinal fluid under normal pressure. A partial block was demonstrated on compressing the jugular veins. The cerebrospinal fluid contained 100 mg. of protein per cmm., and 6 lymphocytes; the Wassermann reaction was negative. Intrathecal injection of 1 c.c. of lipiodol revealed a block at the level of the third thoracic vertebra (*Fig.* 47).

A diagnosis of cord compression by carcinomatous spread from the apex of the lung was made. No operation was performed. The patient went rapidly downhill and died 2 weeks after admission from bronchopneumonia and pyelonephritis.

AT AUTOPSY (P.M., 1943/224).—Almost lobar fibrinous, partly hæmorrhagic, consolidation of the right upper lobe was found. The left upper lobe and the upper parts of the left lower lobe were firmly adherent to the chest wall, notably in the medial parts adjoining the necks of the third and fourth ribs. Here a fairly soft subpleural growth 3 cm. × 3 cm. in diameter was detected in close proximity to the third and fourth thoracic vertebræ, which had been invaded by it (*Fig.* 48). The dura mater was surrounded at the level of the third and fourth vertebræ by tumour tissue, which had invaded the spinal canal through the intervertebral foramina. The spinal cord was not invaded, but was constricted by the thickened dura. There was extensive purulent pyelonephritis. Careful dissection of the lungs, the bronchial system, the pharynx, the œsophagus, and the rest of the organs failed to reveal any evidence of a primary growth.

HISTOLOGICAL EXAMINATION.—The consolidated parts of the right upper lobe showed simple inflammatory changes (confluent bronchopneumonia). A section through the subpleural growth in the third intercostal space showed a large-celled carcinoma with alveolar pattern. In some of the alveoli the cells are of the 'crazy-pavement' type, with intercellular spaces and bridges—a prickle-celled carcinoma. There was, however, no hornification (*Fig.* 49).

FIG. 49.—*Case* 2. Section through the subpleural growth. Squamous-celled carcinoma. No hornification. (× 100.)

The relationship of the growth to the lung was examined in serial sections through various areas of the upper and medial parts of the left upper lobe adherent to the parietal pleura covering the growth. In the parts of the lung adherent to the tumour only an area of dense anthracotic scar tissue with a calcified round focus in the centre contained tumour-cell units (*Fig.* 50). On both sides of the scar symmetrical infiltration was found with nests and alveoli of prickle cells, and it was in these areas alone that hornification could be detected (*Fig.* 51).

Comment.—This case again presents an apparently extrapulmonary prickle-celled carcinoma invading the necks of the ribs, the vertebræ, and spinal canal. This time, however, the growth developed below the pleural dome. The parts of the lung adherent to the growth were free except one area of an old anthracotic scar with a calcified centre. This isolated involvement of an area of scar tissue seems to be more than accidental. Moreover, it was only in this part of the growth that hornification was seen, i.e., changes indicating tissue maturity and absence of anaplasia. It is fair to assume that these areas represent the original site of the growth.

The isolated involvement of a pulmonary scar and the presence of the presumably oldest changes therein are features which this case has in common with the first, and which provide evidence that the tumour originally developed in and around an intrapulmonary scar and not outside the lung.

DISCUSSION

The two cases fall into the group described by Pancoast as "superior pulmonary sulcus tumours", for they exhibit most of the familiar characteristics of these tumours—viz., a primary squamous-celled carcinoma situated in the apical part of the pleural cavity, extending into the bony structures of the pleural dome, notably the ribs and vertebræ, and in this process invading the brachial plexus and the sympathetic trunk, producing pain and paresis in the shoulder and the arm together with a Horner's syndrome.

FIG. 50.—*Case* 2. Survey through scar tissue in the lung adherent to subpleural growth. Diffuse infiltration of scar tissue with squamous-celled carcinoma. In the centre of scar a black calcified nodule. (× 20.)

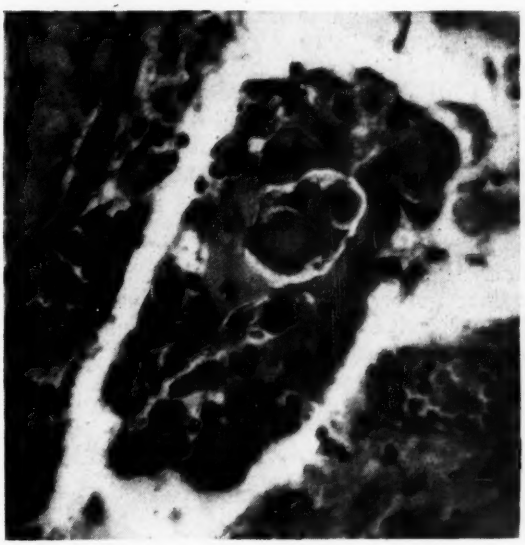

FIG. 51.—*Case* 2. Scar carcinoma of lung adjacent to subpleural growth showing nests of squamous cells with central hornification. (× 165.)

Although Pancoast suggested these criteria, only 2 of the 7 cases described by him were subjected to histological examination, and only one of these showed the picture of a squamous-celled carcinoma. There are indeed but few cases in the literature conforming to these

criteria. Clarke (1934) described 1 case with an extrapleural tumour eroding the ribs and vertebral bodies adjacent to the apex of the lung. A Horner's syndrome with pain in the arms and muscular atrophy was present. Although the tumour was adherent to the lung, there was no evidence of a pulmonary origin. In the absence of a bronchogenic source, Clarke suggested an origin in a branchial remnant. Fried (1935) described 2 cases presenting all the characteristics of a Pancoast tumour. In each case histology showed a squamous-celled carcinoma with no evidence of a pleural or pulmonary origin. In one case the lung was adherent to the tumour and was detached from it with difficulty, although apparently separated from the tumour by the pleura. Fried is of the same opinion as Pancoast and Clarke—that these tumours arise from remnants of the branchial clefts, and he suggested the term 'branchioma' as descriptive of their origin. Graef and Steinberg (1936) recorded 1 case with a typical Pancoast syndrome. The lung was adherent to the apical tumour, but was easily separated without loss of lung substance. The histological structure was that of a squamous epithelioma, and they considered it was not possible to rule out a branchiogenic origin.

Morris and Harken (1940), in a complete review of the subject, described 3 cases which conform to the criteria laid down. They concluded from their study that there does exist at the superior pulmonary apex an epithelial neoplasm which is distinguished from all other tumours common to this region by its lack of origin from any known adjacent tissue or from metastatic foci, and by a histological picture suggestive of an embryonal source.

In all these cases no detailed microscopical investigation by serial sections of the part of the lung underlying the tumour has been made, and therefore the hypothesis of an extrapulmonary origin advanced by these various authors cannot be upheld.

It is difficult to say whether the two cases described by us provide sufficient evidence against the existence of a true extrapulmonary "upper sulcus tumour". We would submit, however, that it is no sufficient to state that the lung and the growth were easily separable "without loss of substance", or that it was "definitely extrapleural", or that there was "infiltration of the apical pleura with freedom of the bronchi and lung tissue". Careful examination of serial sections of the adjacent parts of the lungs is essential before an extrapulmonary origin can be postulated. Although the evidence produced in the two cases described by us indicates an intrapulmonary origin, the tumours form an unusual group presenting characteristic clinical, radiological, and histological features. We agree, therefore, with Pancoast that they deserve to be more widely known as a special entity, and we suggest that 'miniature scar-carcinoma of the lung with involvement of the thoracic inlet' is more descriptive of the pathology than the more general term 'superior pulmonary sulcus tumour'.

SUMMARY AND CONCLUSIONS

Two cases are described in which the Pancoast syndrome was present in association with a tumour at the thoracic inlet. There was no macroscopical evidence of a pulmonary origin.

Serial sections of the lung tissue adjacent to the tumours revealed a miniature scar-carcinoma. This showed the oldest changes—hornification and sebaceous material—and was therefore regarded as the origin of the growth.

Serial sections of the adjacent lung tissue are necessary before a pulmonary origin of the 'upper sulcus tumour' can be excluded.

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ADRENAL VIRILISM

REPORT OF A CASE WITH UNUSUAL FEATURES

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THE problem of the development of abnormal sexual characteristics is complex. The case described here is more complex than usual. Many of the findings are capable of some explanation; the unexplained touch on many problems.

CASE REPORT

HISTORY.—The patient was born in 1903. From birth until puberty the patient appeared, behaved, and was brought up as a normal female child. There were other brothers and sisters of the family who were normal, but cannot now be traced.

1917: At the age of 13–14 years hair began to grow on the face and the voice broke. Menstruation did not start, although it was noted that the external genitalia had developed normally for the age. The general bodily habitus, voice, and facies became so distinctly male in type by the age of 16 years that the patient then changed her Christian name to 'John', donned male attire, left home, and worked, first as a van-boy, and later as a lorry driver.

1925: At the age of 22 years the patient returned to his parents' home suffering from neurasthenia. (The masculine pronoun will now be used when referring to the patient.) The trouble appeared to have developed after a doctor had been called in to treat the patient for influenza and his true condition had become known. Later the family doctor sent the patient to Western Infirmary, Glasgow, for observation in Professor Ralph Stockman's wards.

The following are the notes from the ward journal, additional to the family doctor's letter giving the previous history and affirming that the patient had never menstruated.

"Condition: Neurasthenia secondary to virilism. Pyorrhœa alveolaris. The patient is 4 ft. 11 in. in height and superficially appears to be a man. He lies comfortably in bed so long as his head is supported, but whenever his head is raised from the pillow he closes his eyes and complains of lightheadedness amounting almost to fainting. The breath is very foul, due to a general condition of pyorrhœa. The distribution of hair is male, the beard being abnormally strong. (The patient shaves every second day.) The cranial hair is receding and is of very fine texture. The hands and feet are small and suggest femininity. The external genitalia are apparently of typical female form. Figure and voice masculine; pelvis masculine; gestures and mental outlook suggest femininity.

"June 5: Chloroform. Dr. Martin examined the genitalia. The clitoris has not the normal female shape, but is notched like the male penis. The urethra is of female shape and position. Vagina present with rudimentary cervix, but no definite uterus. Gland palpable in position of right ovary. No signs of testes.

"Complete extraction of teeth was performed at same occasion."

The patient was discharged a few weeks later, his general condition having improved. He left his parents' home shortly afterwards.

1935: The patient was again traced. He was working as a lorry driver and was apparently accepted as a male without any suspicion by his workmates.

1941: The patient returned to the family doctor for a certificate to support his claim as a 'conscientious objector'. He had been working since the outbreak of war as a shipyard labourer. On being interrogated (1943) his fellow workmen and friends at his lodging gave no indication that they even suspected his being abnormal. If he had any psychological upset he managed to keep it hidden. He had no interest in the female sex. The certificate given to him by his family doctor gave the additional information that the patient now menstruated, but the date of commencement was not given.

1943: After a history of a few months' duration of lower abdominal discomfort, ultimately with alternate diarrhœa and constipation, sudden acute illness supervened and the patient was admitted to the Western Infirmary, Glasgow, as an 'acute abdomen'. The doctor who sent the patient to the infirmary had noted that there was a carcinoma of the right breast, which the patient stated had been present for two years.

Laparotomy was performed a few hours after admission to hospital and pus was evacuated from the pelvis. A sloughing mass of tumour in connexion with an ovarian dermoid cyst was found by the surgeon. The patient died a few hours after the operation. Autopsy was performed twelve hours later.

The only additional information obtained from the patient at hospital was the statement that he had menstruated all his life. This must be taken with reserve as the patient was *in extremis*. There is post-mortem evidence that the patient did menstruate, and it is known that he menstruated in 1941. It must be presumed, therefore, that the patient started to menstruate some time after 1925, when he was examined in the Western Infirmary.

POST-MORTEM EXAMINATION.—

External Appearances.—Apart from the external genitalia and breasts, the subject had the facies and bodily habitus of a male of rather slender build and of small stature (5 ft. 1 in.). There was little subcutaneous fat and the body and limbs presented an athletic appearance. The hair of the head was of fine texture. There was complete baldness of the frontal area, and a heavy growth of coarse, recently shaven hair on the shaving areas of the face; hair growth was not marked on the chest or limbs. The abdominal and genital hair were of female distribution. The breasts appeared as unusually circumscribed elevated plaques about 8 cm. in diameter and 2·5 cm. thick. The nipples were prominent and showed no displacement. *The right breast* had a uniform hard consistence. *The left breast* was less hard and had the characteristic knobby consistence of fibrocystic mastopathy. Both breasts were very easily removed by blunt dissection and traction. Section of the right breast revealed a uniform dense white, hard, fibrous tissue; section of the left breast showed similar appearances, but with numerous small cysts throughout. No axillary glands or other evidence of lymphatic tumour spread from the breasts were present.

Thorax and Abdomen.—There were large quantities of pus in the peritoneal cavity, especially in the pelvic region. The coils of the small intestine were glued together by light fibrinous adhesions.

The *heart*, 230 g.; *liver*, 1000 g.; *spleen*, 90 g., were slightly smaller than one would expect in a male, even allowing for the build and stature of the subject. The *kidneys* weighed 120 g. each. No abnormality was detected in the cardiovascular, urinary, skeletal, or alimentary systems, except for tumour invasion of the colon, which will be referred to later. The lungs showed congestion and œdema.

The *thyroid* (15 g.) showed natural tissue. No thymic tissue was noted in the mediastinum.

The *liver*: Eight white nodules, from miliary size up to 2 cm. in diameter, having the typical appearances of secondary carcinoma were present in the liver.

The *right adrenal gland* (18 g., 3 cm. × 3·5 cm.) was represented by a body with four roughly triangular surfaces. The bulk of the specimen was taken up by a hard mass of calcareous and ossified material replacing the medulla. The flat surfaces of the hard mass were clothed by a thick fibrous capsule containing small islets of bright yellow adrenocortical tissue. At the free edges the fibrous capsule was reflected off to form an integument for thickened ridges of adrenal cortex. (*Fig.* 52.)

The *left adrenal gland* (5·5 g.) presented natural appearances; the cortical tissue was prominent, but not definitely increased.

Para-aortic glands: In the region of the cœliac axis there was a conglomerate mass of enlarged glands, from 0·5 to 2 cm. in diameter, irregular in shape, fibrous, and containing many chalky white calcareous nodes.

The *ovaries*: Both ovaries were represented by dermoid cysts filling the pelvis, the right 11 cm. in diameter, the left 8 cm. These consisted of cavities

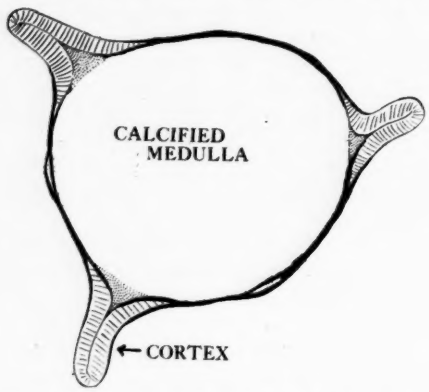

FIG. 52.—Diagram of section of right adrenal body.

filled with hair and inspissated sebaceous material, with smooth thin walls. In each there was an area of thickening in the wall incorporating ovarian tissue. In the right dermoid the ovarian tissue was extensive, and contained numerous blood-vessels, small cysts containing clear fluid, and a large corpus luteum stretched over an area of 3·5 cm. in diameter and 0·5 cm. in maximum thickness. In the left cyst the

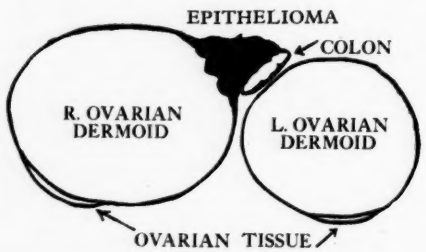

FIG. 53.—Diagram of ovarian dermoids.

ovarian tissue was confined to an attenuated area 2 cm. in diameter and presenting as white ovarian stroma without other macroscopical detail. Postero-internally the interior of the right cyst was heaped up and irregular. From here a large mass of pale tumour tissue extended backwards and inwards to invade the wall of the colon at the brim of the pelvis. Numerous yellow areas of necrosis were present in the tumour mass and, near the colon, there was sloughing of large areas with loculi of pus in the tissues. This was evidently the source of the peritonitis. (*Fig.* 53.)

The *uterus*, 5 cm. long from neck to fundus and 2·5 cm. in maximal thickness, was small, but had a thick layer of endometrium (*Fig.* 54). The cervix was small.

Head: The *brain* (1050 g.) showed a general atrophy, with widening of the sulci and ventricles and excess of cerebrospinal fluid. No other abnormality was detected. The pineal body and the pituitary gland were of natural size and appearance.

HISTOLOGICAL EXAMINATION.—

The Adrenal Glands and Calcified Para-aortic Glands.—The adrenal glands and the calcified para-aortic glands require joint consideration as they present associated abnormalities.

The capsules of the para-aortic glands show fibrous thickening with lobulation by thick fibrous trabeculæ. The calcified areas, of amorphous appearance, are in some cases completely invested by fibrous tissue, in others associated with uncalcified caseous material. The whole presents a picture indistinguishable from effete tuberculosis (*see Fig.* 57). While the regressive

FIG. 54.—Transverse section of uterus. Note the thick endometrium. H. and E. (× 3.)

changes are in most areas complete, a few small cellular follicles with central caseation, indistinguishable from tuberculous follicles, are present. Although tubercle bacilli have not been demonstrated, it is considered that it must be taken that all the latter appearances represent tuberculosis with almost complete healing. The same process appears to be a reasonable explanation for the large calcified and bony mass taking up the right adrenal medulla. The picture is the same, except that no cellular follicles are present and there is much imperfect bone formation in the calcified amorphous material. There is no organoid differentiation to indicate the existence either of a simple tumour of bone or of degeneration in a bone-bearing teratoma. The flat surfaces of the bony mass in the right adrenal are clothed by a thick fibrous capsule including small pseudo-adenomatous formations of adrenocortical epithelium. The thickened tissue reflected off at the angles of the right adrenal body (*Fig.* 55) presents the general gross characters of adrenal cortex and shows all three histological zones. But, scattered throughout, are collections of altered adrenocortical epithelium. In some of these pseudo-adenomatous masses the cells are large and show gross vacuolation; in others they have a solid non-vacuolated cytoplasm (*Fig.* 56). The left adrenal gland shows no abnormality.

Nodules of epithelial tissue are present in the conglomerate mass of calcified cœliac glands. They are encapsulated by fibrous bands. The cells are arranged in columns supported by loose stroma, with the malignant epithelium in the right breast and the hepatic metastases, the cells of the latter being smaller and having vesicular, oval nuclei and scanty, loose, pale-staining cytoplasm. The fuchsinophil granules

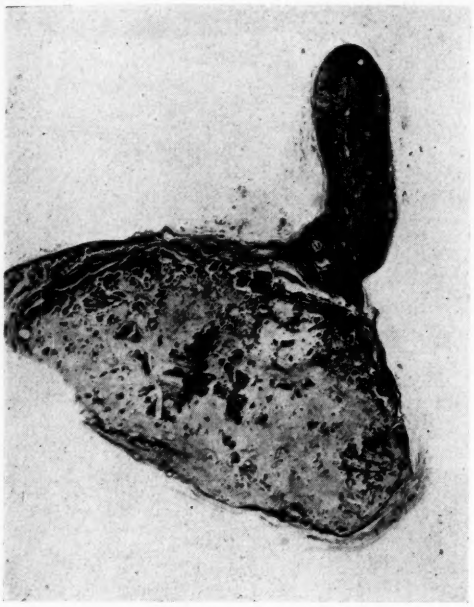

FIG. 55.—Section of part of right adrenal, showing thickened ridge of adrenal cortex and the calcified and ossified medulla. H. and E. (× 1·5.)

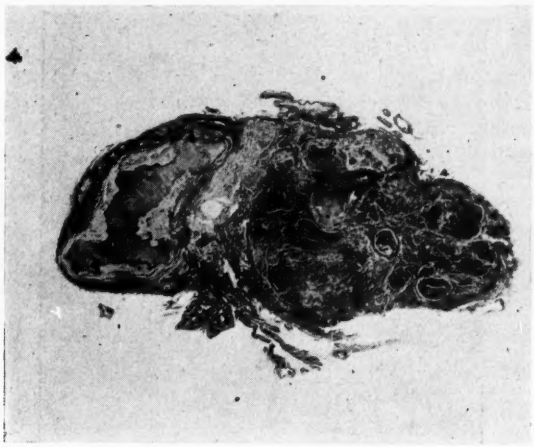

FIG. 57.—Para-aortic gland, showing node of calcified effete tuberculosis on left and foci of epithelial tissue (dark masses) circumscribed by fibrous capsules (white rings). H. and E. (× 4.)

of Vines (referred to in the discussion) were not found in the cœliac epithelium or in the adrenal cortex.

Ovarian dermoids: The cyst walls consist of thin epidermis with hair follicles and accessory skin glands.

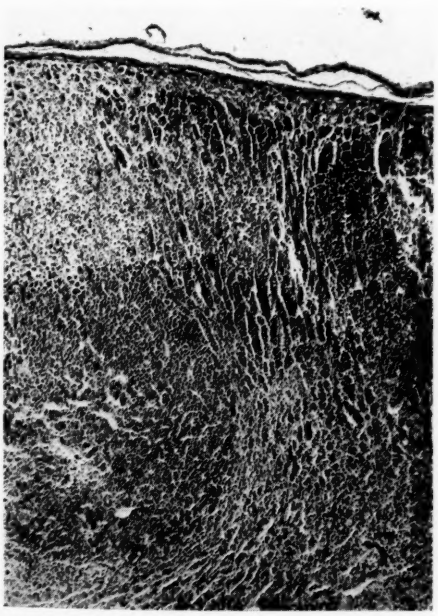

FIG. 56.—Cortex of right adrenal. Note the disturbance in architecture. H. and E. (× 30.)

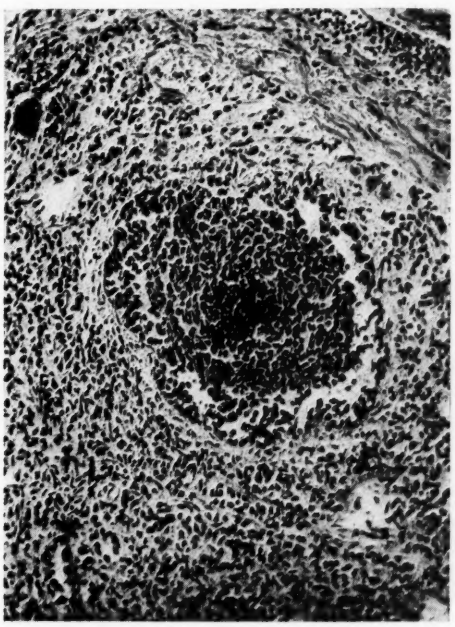

FIG. 58.—Area from *Fig.* 57, showing adrenocortical epithelium in loose columns and in whorl encircling lymphocytes. H. and E. (× 115.)

small focal accumulations of lymphocytes in places. They are polygonal and have dense eosinophil cytoplasm which, with the oil-immersion lens, can be seen to be finely granular. The nuclei are central, and hyperchromatic. No mitoses are present. (*Figs.* 57, 58.) This epithelium is sharply distinguished from

A few small islets of cartilage are the only other elements found on extensive examination. The mass of tumour arising in the heaped-up area in the right cyst wall and extending in a large mass into the colon is a squamous epithelioma; it is well differentiated,

with large cell-nests having prominent keratinized centres. While well differentiated in mass, the basal cells are large and aberrant. The tumour extends through the wall of the colon to the basement membrane of the mucosa (*Fig.* 59). The infiltrated bowel musculature and the region of the colon above show hypertrophy, a degree of chronic obstruction apparently having been present. The ovarian tissue incorporated in the wall of the right cyst equals a normal ovary in amount, while that of the left is slightly less. Examples of primordial follicles, early follicle formation, a few small corpora albicantia, and many small atretic follicles have all been recognized in addition to the large macroscopic corpus luteum previously referred to (*Fig.* 60).

Uterus: A well-circumscribed intramural fibroid

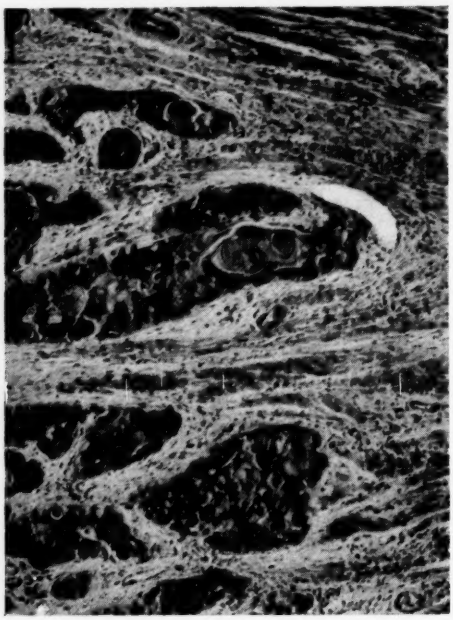

FIG. 59.—Epithelioma invading muscular coat of colon. H. and E. (× 115.)

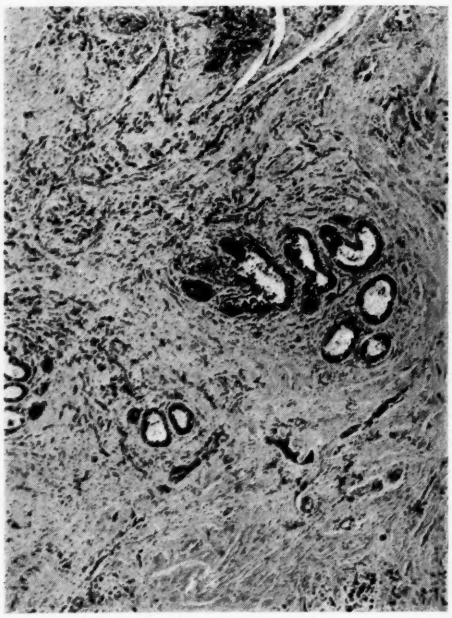

FIG. 61.—Right breast showing malignant infiltration of dense fibrous stroma and also duct epithelial hyperplasia. H. and E. (× 12.)

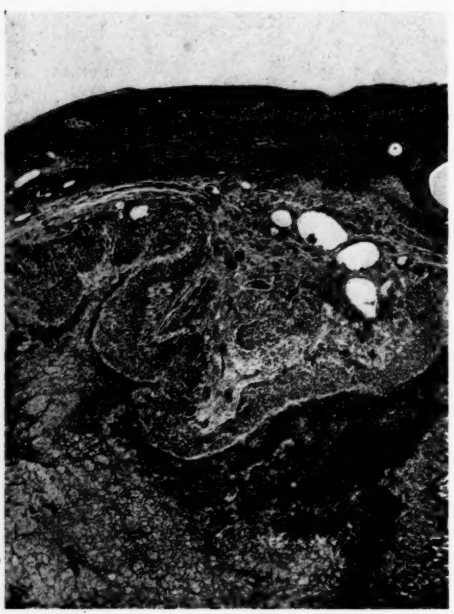

FIG. 60.—Part of large corpus luteum, right ovary; note the well-defined layer of luteal cells. H. and E. (× 7·5.)

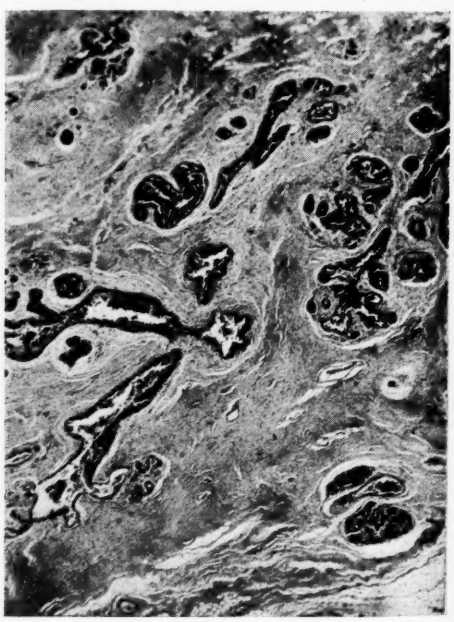

FIG. 62.—Left breast, showing dense stroma and epithelial hyperplasia in cystic ducts. H. and E. (× 12.)

takes up the whole thickness of the uterine wall at one point. The endometrium shows normal premenstrual secretory characters.

Mammary glands: Both breasts show dense hyaline fibrosis. The basement membranes of many of the ducts and acini show hyaline thickening and also peripheral whorled fibrosis. In some of the ducts and acini this obliterative process has resulted in destruction of the epithelium. In others there is epithelial hyperplasia with the production of intraduct and intra-acinar tumour of both solid and cribriform type. In the right breast the intraduct tumour has broken through, with the production of universal injection of the tissue spaces with tumour cells (*Fig.* 61), but there is only marginal infiltration of the surrounding fatty tissue. Cystic change in ducts and acini is conspicuous in the left breast. This is associated with many areas of intraduct tumour, but there has been no break through with the development of frank malignancy (*Fig.* 62).

The *hepatic tumour nodules* show characters consistent with metastases from the right breast. The tumour epithelium consists of small cells with loose scanty cytoplasm. The epithelium, associated with moderate stroma production, shows a tendency to adenomatous formation. The growing edge presents the characters of tumour invasion and there is no suggestion that the masses represent ectopic or metastatic adrenocortical epithelium.

The *pituitary gland* was examined by methods previously described (McLetchie, 1944, a). The gland shows a normal gross structure; the pars intermedia is represented by a single cleft. The basophils of the anterior lobe are not numerous but are within normal limits in relative proportion. The basophils show normal granularity, vacuolation is inconspicuous, and the hyaline lesion of Crooke is absent. The acidophils and chromophobes present no abnormality.

Much of the *pineal* is calcified; no abnormality is detected.

SUMMARY OF POST-MORTEM FINDINGS.—Spare virile habitus with facial hair of male type; female external genitalia and enlarged clitoris; mammary carcinoma with hepatic metastases; bilateral ovarian dermoid cysts; epithelioma arising in right ovarian dermoid invading colon, with production of peritonitis; ovarian tissue, including a large corpus luteum, in wall of dermoids; right adrenal represented by ridges of thickened cortex upon a calcified and ossified medulla; epithelial tissue incorporated in mass of calcified cœliac glands; small uterus with thick endometrium.

DISCUSSION

The Adrenal Abnormality.—The association of the development of virilism in the female with adrenocortical abnormality has long been known. The subject has been extensively studied and reviewed by Broster and Vines and their coworkers (1938). The case described is a good example of the condition. Here there was the development of the voice, bodily habitus, and facial hair distribution of the male, and enlargement of the clitoris, in an apparently normal female subject. The changes were so marked that within a few years of their first appearance the patient masqueraded successfully as a male, and later survived the 'rough and tumble' of a Clyde shipyard without incident. The alterations began at puberty. Broster and Vines describe how marked sex-reversal may be when the alterations occur early in life, whereas, if occurring later, due to the loss of plasticity of the tissues, the changes are not so marked.

Broster and Vines describe numerous cases with adrenocortical hyperplasia. In the present case the adrenocortical abnormality is of some complexity. The right adrenocortical tissue is certainly thickened, but it is considered that the anatomical peculiarity of the specimen suggests that, in the beginning, there was a uniform thickening of the adrenal cortex, and that later the medulla was replaced and expanded by a morbid process resulting in atrophy of much of the cortex and leaving only the peculiar heaped-up projections of cortical tissue. But this is not an end to the adrenocortical abnormality. It is considered that the epithelial nodes embedded in the effete tuberculous mass in the cœliac region represent ectopic adrenocortical tissue. The tissue bears a close resemblance to an adenoma of ectopic adrenal tissue associated with virilism previously encountered. I find no evidence that it is a metastatic tumour. The ovarian tumour is an epithelioma; the breast cancer has different cytological characters from the cœliac tissues. In extensive sectioning no evidence of malignant tissue has been found in the cœliac lymphatics. The cœliac epithelium, well circumscribed by fibrous and calcareous tissue, has evidently been long resident there and shows, rather than invasive characters, retrogression before an advancing fibrotic process.

Thus, from its character and arrangement, it is considered that the cœliac epithelium is ectopic and not metastatic and that it is ectopic adrenocortical tissue. Moreover, it has been previously more extensive, and has been reduced by a chronic tuberculous process in neighbouring glands. The nature of the morbid process which has occupied and expanded the right adrenal medulla is more obscure. There is no evidence to indicate the existence of a bone-bearing teratomatous mass. It is considered that a now effete tuberculous process is the most reasonable explanation. But this is in dispute, and, in view of the other anomalies of development present, degeneration in some congenital malformation cannot be excluded as an explanation for the adrenal medullary mass. Either way the general argument remains—namely, that in the right adrenal a thickened adrenal cortex has been reduced by the evolution of a chronic process in the medulla and that in the cœliac region ectopic adrenocortical tissue has been reduced by a chronic process more obviously tuberculous in origin.

Ectopic adrenocortical tissue is not unknown in adrenal virilism. McLetchie and Scott (1944) have described an adrenocortical tumour in the tail of the pancreas associated with bilateral adrenocortical hyperplasia, and Kolodny (1934) has also described a case of virilism with a carcinoma of ectopic adrenocortical tissue in the cœliac region.

Vines (1938) has claimed that the essential abnormality in adrenal virilism is the presence of fuchsinophil granules in the adrenocortical epithelium. He relates these granules to a special androgenic activity of the adrenals which is normally dormant in adult life, but is long persistent in the male fœtus and only transient in the female fœtus. Vines used a special staining technique on fresh adrenal tissue. Difficulty had been found in obtaining selective differentiation with Vines' stain, and in applying the stain to post-mortem tissues. Nevertheless, in a previous case (McLetchie and Scott, 1944), granules as fuchsinophil as fibrin were found in adrenal tissue (hyperplastic cortex and cortical tumour), while such granules have never been found in tumours from other sources using the same staining technique—McFarlane's picro-mallory (McFarlane, 1944). In the present case the tissues had the additional handicap of requiring decalcification, and although no granules were found, Vines' hypothesis can only be adequately assessed on the examination of fresh tissue. Varying results have been reported by other workers, and the present position is obscure.

Grollman (1936) has attempted to relate the activity of the adrenals in virilism to the function of a special " androgenic " zone distinct from the cortex proper. In the mouse at certain stages there is a prominent zone of epithelium—the juxta-medullary or X-zone—between the medulla and cortex proper, which has different characters from the cortex. A similar zone is present in the human fœtus, and Grollman claims that virilism in the female follows from a resurrection of this tissue. No illustrations of the hyperplastic adrenals of virilism have been published showing more than a thickened cortex proper, and I have found no evidence of the existence of such a zone in the adult human or in cases of adrenal virilism. Furthermore, some virilizing adrenal tumours show a striking resemblance to true adrenal cortex. In tumour production de-differentiation is the rule, and it would be a contradiction of our general knowledge of tumours to assume that such growths arose from a tissue having different characters from the cortex proper. Grollman also claims that Vines' granules are an attribute of the special juxta-medullary tissue. Vines' granules have only been described in the cells of the cortex proper and not in a new zone. In the present case zones of altered character are present in the thickened adrenal cortex. These are not constant in virilism and in this case they are more probably related to the presence of the medullary mass, with attendant alterations in vascular supply to the cortex, rather than morbid manifestations of a special altered function. It is considered that present evidence does not allow of more than the assumption that the thickened adrenal cortex of virilism is an attribute of simple hyperfunction. This may, however, be to the exclusion of certain functions of the adrenal cortex. Thus the adrenal cortex has a high ascorbic acid content, and also has appreciable quantities of other vitamins. One of the most constant early signs of adrenal virilism is severe facial acne vulgaris. This may be due to the loss of that function of the adrenal cortex related to vitamins.

The Ovarian Tissue.—It should be noted that a gynæcologist palpated a " gland " in the right ovarian region, when the patient was twenty-one. Presumably this was the right ovarian dermoid. At autopsy the patient had abundant ovarian tissue in the wall of the right dermoid, and it cannot be postulated that the presence of the dermoids interfered with the hormonal function of the ovaries. The dermoid cysts can thus only be regarded as part of a complex congenital anomaly not specially related to the virilizing process.

The Development of Menstruation.—The development of menstruation in so complete a case of virilism presents a problem in itself. Precise knowledge of the history is not as complete as one would have wished. Nevertheless, it is clear that from puberty until the age of 22 the subject did not menstruate and that, at the end of that period, a gynæcologist reported that the cervix was rudimentary and that there was no definite uterus. From the patient's statements it would appear that menstruation had been present for many of his subsequent eighteen years of life. This seems more plausible on consideration of the autopsy findings of a small but by no means rudimentary uterus, complete with a thick layer of secretory endometrium (and a fibroid), while there is a large corpus luteum in the right ovary. I consider that the establishment of menstruation, the growth of the uterus, and the presence of a large corpus luteum in the ovary at autopsy have been brought about by reduction of the adrenal tissue, cortical and ectopic, by the chronic obliterative processes referred to. The obliterative process is of old standing, and this is consistent with the establishment of menstruation many years ago.

Though it is presumed that a reduction of the excessive adrenocortical tissue was sufficient to allow of the establishment of menstruation, this did not permit of a reassertion of other feminine characters. It is considered that this is mainly due to loss of plasticity of the tissues with age and indicates the hopelessness of surgical intervention once these abnormal conditions are long developed.

The Two Malignant Tumours.—The presence of two undoubtedly malignant tumours is rare. In the present case there is in a subject of 40 years a scirrhous carcinoma of the right breast and an epithelioma arising in the wall of an ovarian dermoid of otherwise simple structure. In both cases malignancy is undoubted; the epithelioma having produced a large mass of tumour with invasion of the colon; while in the right breast there is widespread scirrhous carcinoma associated with hepatic metastases presumably blood-borne. At present sex hormones, especially the œstrogens, are playing a prominent

part in the production of experimental cancer in general and of experimental mammary cancer in particular. There can be no doubt that the patient had a very abnormal endocrine make-up and it is attractive to suggest that this hormonal upset was an important factor in the development of the two malignant growths. At the present time the assay of hormones in the human subject is in an embryonic stage and there has been little correlation of the empirical data so far obtained with physiological and pathological phenomena. Nevertheless, the presence of two malignant tumours in a subject with undoubted endocrine upset may at least serve as a stimulus to the pursuit of knowledge in the field of endocrine assay in the human subject, with applications far beyond the study of rarities such as the case described. In regard to this question many senior surgeons will recall the practice of ovariectomy in association with mammectomy for breast cancer.

PROBLEMS OF DIAGNOSIS AND TREATMENT

Broster and Vines (1938), Walters, Wilder, and Kepler (1934), and others have reported successful amelioration of the condition of virilism by removal of the larger adrenal in cases of adrenocortical hyperplasia, and of adrenocortical tumours when present. Intervention must be as early as possible, and, indeed, is inadvisable when the condition is of long standing, as is obvious in the present case, where reduction of the offending tissue has made the patient's condition worse by initiating menstruation.

In the event of laparotomy the surgeon must be aware that the offending tissue may lie outside the adrenal glands proper. In the present case there is ectopic tissue in the region of the cœliac axis, and I have already cited cases with adrenal rest tumours in the pancreas and in the cœliac region. Glynn (1911) quotes a number of cases of the allied condition of pseudo-hermaphroditism with large adrenocortical rests in the broad ligament. It must also be remembered that the rarer arrhenoblastoma group of ovarian tumours produces a syndrome indistinguishable from adrenal virilism. It is to be noted that claims have been made that certain virilizing tumours of the ovary arise in ectopic adrenocortical tissue (Novak, 1941).

A recent paper by Anderson, Hain, and Patterson (1943) indicates that early diagnosis of the adrenal abnormality associated with virilism may be made with the finding of high pregnanediol and 17-ketosteroid values in the urine and they recommend that these estimations be made in all cases of secondary amenorrhœa to ensure the early diagnosis of such cases.

While early diagnosis of the condition of virilism is advisable, if surgical intervention is going to be of any avail, it must be recognized that in its early history Cushing's syndrome is indistinguishable from adrenal virilism, and accordingly the intelligent management of these cases requires an understanding of the morbid basis of Cushing's syndrome.

CUSHING'S SYNDROME

In 1932 Harvey Cushing described the multiglandular syndrome of pituitary basophilism which now bears his name. The syndrome was associated with the development of obesity, sometimes painful and sparing the limbs, hypertension, and vasculo-cutaneous alteration, with the development of characteristic striæ, glycosuria, hyperglycæmia, osteoporosis, and polycythæmia, and in the female with amenorrhœa and hirsutism of male type. This contrasts with the condition of virilism as exemplified by the present case, where there was maintained a spare virile habitus without the development of obesity or other signs of multiglandular disease. Nevertheless, Cushing's syndrome takes time to develop and in its early history there may be no more than amenorrhœa, slight roughening of the features, and slight hypertrichosis. Such a case has been reported by McLetchie and Scott (1944), where, after a history of amenorrhœa and hypertrichosis, the patient, a woman of 25, died in coma. At autopsy, in addition to an adrenal carcinoma, such gross alterations were found in the basophils of the hypophysis that it left no doubt that, had the patient lived longer, there would ultimately have been declared a fully developed Cushing's syndrome.

Cushing attributed the syndrome to a basophil adenoma of the anterior pituitary, though he also stated that he believed that the syndrome could equally well be produced by an adrenocortical tumour. Later the precise pathological definition of the condition became obscured, in that cases of clinically undoubted Cushing's syndrome were described with a bewildering array of findings; thus we have the basophil adenoma of the hypophysis, and in one case a metastasizing carcinoma of the basophils; adrenocortical adenoma and more commonly carcinoma; and cases of thymic tumour. It is to be noted that these lesions are not unconnected, in that the basophil adenoma is usually associated with frank adrenocortical hyperplasia; the adrenocortical carcinoma sometimes with basophilia (relative increase in the basophils), and the thymic tumour with adrenocortical hyperplasia. However, in addition to the above pathological types, there were added cases with no tumour anywhere and (it was claimed) a normal hypophysis on serial sectioning, and also cases with small chromophobe or 'indeterminate' adenomata in the anterior pituitary (Cohen and Dible, 1936; McLetchie, 1944, b; Cameron, 1940; Freyberg, Barker, Newburgh, and Coller, 1936). In 1935 Crooke showed that whatever the pathological type there was a constant and special abnormality of the basophil cells of the hypophysis, namely, the replacement of the granular cytoplasm of the basophils to a varying degree by a refractile hyaline cytoplasm. Basophil

hyalinization was a rare and inconspicuous finding in conditions other than Cushing's syndrome. Crooke's findings have been verified and conspicuous basophil hyalinization described in a case where there was no endocrine tumour (McLetchie, 1944, b). Crooke maintained that since basophil hyalinization was associated with a normal nucleus, the lesion represented the anatomical basis of an abnormal function of the basophils which was the essential abnormality of Cushing's syndrome. This well-substantiated hypothesis was highly acceptable on general grounds, since it united an otherwise varying pathology associated with a constant multiglandular symptomatology, in itself highly suggestive of a constant hypophysial abnormality. Moreover, Crooke's finding distinguished the syndrome pathologically from adrenal virilism, in that in the latter he did not find basophil hyalinization.

Later Severinghaus (1938) and others reported that basophil hyalinization in cases of Cushing's syndrome was commonly associated with nuclear breakdown of a curious character; ultimately, the nucleus appeared as a large blister taking up most of the cell and leaving only a fine peripheral rind of hyaline cytoplasm. Despite this gross nuclear change, cell dissolution was not described. It would appear that the American school favoured the view that hyalinization merely represented a process of cell death in the basophils and could not represent a special functional abnormality. Since then it has been shown that the appearances first noted by Severinghaus are produced by gross cytoplasmic vacuolation and that the nuclei are intact though they may be grossly compressed and scalloped by the multiple cytoplasmic vacuoles. Moreover, these appearances are inconstant in pituitary basophilism and sometimes not present even when basophil hyalinization is extreme (McLetchie, 1944, b).

On the basis of these and other findings a more unified conception of the pathology of Cushing's syndrome has been put forward; namely, that: (1) Cushing's syndrome is the attribute of hyperactivity of the basophil cells of the hypophysis and of the adrenal cortex, and (2) hyalinization of the basophil cells of the hypophysis is a manifestation of hyperfunction of these cells. Thus it is considered that the basophil adenoma, when present, is the primary anatomical abnormality, while the accompanying adrenocortical hyperactivity is commonly expressed in frank adrenocortical hyperplasia; the adrenocortical carcinoma produces basophil hyperfunction which is always expressed by hyalinization and sometimes also by relative increase of the basophils (basophilia). In the case of the thymic tumour the probable sequence of events is more obscure, but is correlated with the other types in that there is always basophil hyalinization (hyperactivity) and adrenocortical hyperplasia (hyperactivity); while in cases with no endocrine tumour it is assumed that there is either generalized basophil hyperactivity (there is conspicuous basophil hyalinization) as a primary factor, or that the primary factor is adrenocortical hyperfunction (there is frequently adrenocortical hyperplasia). Small chromophobe adenomata and excessive vacuolation of the basophils in the hypophysis are regarded as secondary phenomena (McLetchie, 1944, b).

Since adrenal lesions unassociated with demonstrable pituitary change are associated with virilism, while, on the other hand, when associated with hyalinization of the basophils of the hypophysis Cushing's syndrome develops, it may be asked: "What determines the difference?" McLetchie (1944, b) has put forward the hypothesis that this may only be a question of degree, virilism being commonly associated with adrenal hyperplasia while adrenocortical tumour usually leads to the development of Cushing's syndrome. In other words, it may be that only a great degree of adrenocortical hyperfunction can stimulate a complementary basophil hyperfunction equivalent to a basophil adenoma. While Anderson, Hain, and Patterson (1943) have described a giant adrenal tumour associated with virilism, and proved at autopsy not to involve basophil hyalinization, this does not exclude the above theory, since most of the tumour was necrotic, quite apart from the general criticism that tumour tissue of endocrine origin varies greatly in its endocrine activity, and, therefore, size alone is not an absolute function of activity.

Thus in the assessment of any case of early masculinization, adrenal, hypophysial, thymic, and ovarian abnormality all require consideration. If a spare virile habitus has been maintained for some time, primary adrenal or ovarian abnormality is likely. If signs of multiglandular upset develop, e.g., obesity or glycosuria, an adrenal, thymic, or pituitary tumour is possible.

While there are admittedly great gaps in our knowledge of the interrelationship of the endocrine glands, the final elucidation of the problem must depend on many methods of approach and the surgeon has his part to play. He may do not more than perform laparotomy in a case of virilism, and remove an ovarian or adrenal tumour, to achieve a dramatic ameliorization of the condition. On the other hand, a thymic tumour may be found radiologically, and it remains to be seen what the result of the removal of such a tumour will be, for this has never been done. Indeed, the position of the thymus in the inter-endocrine relationships under discussion is the most obscure, and occupies a somewhat anomalous position. Clinically Cushing's syndrome is almost the exact opposite of Addison's disease. For this there is pathological correlation. The question of hyperfunction of the basophils of the hypophysis and of the adrenal cortex in Cushing's syndrome has already been mentioned; in Addison's disease the opposite obtains in that destruction of the adrenal cortex is accompanied by gross diminution of the basophil cells of the

hypophysis (Crooke and Russell, 1935). No apparent correlation exists in the case of the thymus, for in Cushing's syndrome there may be a thymic tumour, while in Addison's disease thymic hyperplasia is common.

It may be that on removal of the larger hyperplastic adrenal in what appears to be an early case of virilism the case will proceed to the development of a full Cushing's syndrome, and only autopsy will reveal the underlying cause—a basophil adenoma of the hypophysis—for it is not revealed radiologically. This type of case has been treated by insertion of radon seeds into the pituitary fossa (Pattison and Swan, 1938). It is possible that in the investigation of the urinary hormones of such a case means will be found of differentiating cases of primary pituitary and adrenal abnormality. All that and more remains to be seen.

Broster and Vines state that in some of their cases of virilism no endocrine gland abnormality was detected, though amelioration of symptoms may sometimes be obtained by removal of the larger adrenal. It should be appreciated that Broster and Vines' survey goes quite beyond the type of case which most surgeons will deal with, namely, the sudden appearance of progressive signs of virilism in a previously normal female. Here there is likely to be an obvious lesion. Equally well, the numerous factual abnormalities which have had to be mentioned in this assessment, will make it very obvious that in so complex a system abnormality productive of virilism may well arise more subtle than our present knowledge could elucidate. But if the ultimate analysis has to depend on a future development of the assay of hormones the basis of interpretation must rest on the correlation of hormonal assay in cases with a known lesion. This will only be arrived at by co-operation between the endocrinologist, the surgeon, and the morbid anatomist.

SUMMARY

A case of virilism is described. The condition developed at puberty in an apparently normal female child. While male characteristics developed to a striking degree, the patient menstruated in the latter part of her life. Death occurred at the age of 40 years from peritonitis. At autopsy the following abnormalities were found: (1) The right adrenal cortex was thickened and there was ectopic adrenocortical tissue in the region of the cœliac axis; both tissues had been reduced by a chronic obliterative process. These were considered to be the essential abnormalities determining the condition of virilism, and their reduction the factor which allowed the development of menstruation, and explained the finding of a large corpus luteum in the right ovary and a thick endometrium at autopsy despite the striking male facies and habitus. (2) Mammary carcinoma with hepatic metastases; bilateral ovarian dermoid cysts, epithelioma arising in the wall of the right dermoid and infiltrating the colon, with production of peritonitis. The problem of the interrelationship of all of these abnormalities is discussed. Attention is drawn to other conditions which may give rise to masculinization in the female.

It is a pleasure to record my thanks to my colleagues, Lt.-Col. Eric Gerstenberg, R.A.M.C., and Lt.-Col. W. L. Lamb, T.D., R.A.M.C., for criticism; to my former colleagues, Mr. Wm. Penny and Mr. Wm. Carson, of Glasgow University Pathology Department, for cutting some hundreds of sections at short notice; to my friend the late Mr. John Kirkpatrick for photomicrography; to Mr. J. Mill Renton, Western Infirmary, Glasgow, and Professor Ralph Stockman for permission to publish clinical details; to Dr. Gibson, of Old Kilpatrick, the patient's family doctor, for his interest and co-operation, and to Dr. Marion Gilmour for assistance at the autopsy.

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SHORT NOTES OF RARE OR OBSCURE CASES

MAYDL'S HERNIA

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THE strangulation of a W-loop of bowel in a hernial sac, described by Maydl, is fortunately rare, for the prognosis is grave in this type of case. There are several factors which contribute to the gravity of the situation. The passage of four lengths of bowel side by side through the neck of the hernial sac determines a tight constriction, which often leads to gangrene of the bowel. The pressure of a strangulated loop of bowel in the general peritoneal cavity, viz., the middle segment of the W-loop, favours the onset of peritonitis. Moreover, the middle segment of the W-loop is usually long, and the release of the constricting ring is likely to be followed by the absorption of the contents of an unusually long stretch of strangulated bowel, an absorption which may give rise to a biochemical crisis of the first magnitude. In the case where the bowel is gangrenous and the loops long, the resection of so great a length of bowel will cause anxiety as to the subsequent powers of assimilation of the patient. For these reasons the record of a case of Maydl's hernia is likely to be of interest.

CASE REPORT

HISTORY.—K. K. P. A., male Sinhalese, aged 30 years, was admitted to the General Hospital, Colombo, on Aug. 5, 1943, on account of a strangulated right inguinal hernia. The hernia had been noted for the past eight years; it had strangulated for the first time four years ago and an operation was performed for this at another hospital. The patient had left hospital in fourteen days, but the hernia had recurred in a month, and had been present since that time, although without trouble till the onset of the present strangulation twenty-four hours previously. The patient was in severe pain and a tense swelling reached all the way down the inguinal canal to the scrotum, indicating a strangulation at the internal ring. The temperature on admission was 101° F.

OPERATION.—An operation was performed under light percaine spinal anæsthesia. An incision was made over the inguinal canal dividing the external oblique aponeurosis, and the hernial sac was opened. An offensive-smelling, blood-stained serum welled out, and a loop of flaccid, green small intestine was seen in the hernial sac. Behind this loop was a second loop of intestine, also in the hernial sac, which was plum coloured from congestion. The conjoint tendon was retracted and the fibrous ring at the neck of the hernial sac divided, releasing the strangulation. On delivery of the bowel, a long loop of flaccid, green small intestine was drawn out of the peritoneal cavity, and offensive-smelling brown serum flowed from the peritoneal cavity. The two loops of bowel in the hernial sac were continuous with the strangulated intraperitoneal loop and on delivery it was found that in all 5 ft. of bowel was involved—4 ft. 3 in. of flaccid, green, gangrenous ileum, followed by 9 in. of plum-coloured ileum, terminating 4 in. from the ileocæcal valve. The cæcum was exteriorized during this exploration. In view of the gangrene of the ileum, resection was inevitable, and 5 ft. of the bowel was resected, continuity being restored by end-to-end anastomosis, using a single layer of catgut which commenced with a Lee's suture at the mesenteric angle, continued as a through-and-through suture for the posterior wall of the anastomosis, and ran on as a continuous Connell suture for the anterior wall. By this arrangement of the sutures, sero-serous apposition was obtained on both anterior and posterior walls of the anastomosis (*Fig.* 63).

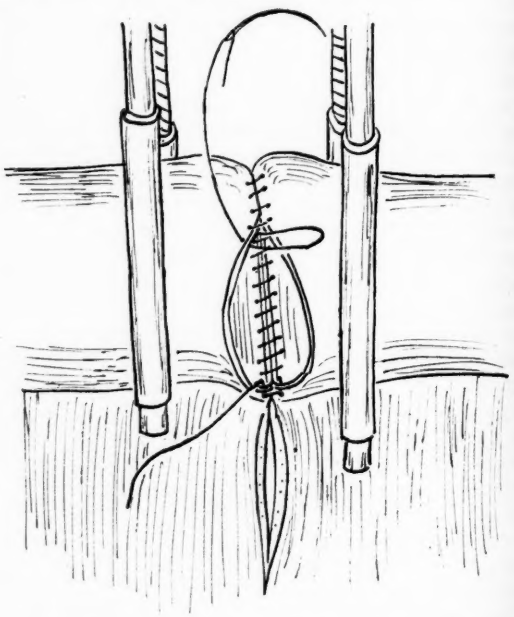

FIG. 63.—Shows method used for one-line suture of intestine, giving end-to-end anastomosis with sero-serous apposition front and back.

While this anastomosis was about to be performed the anæsthetist observed that the condition of the patient had suddenly deteriorated—his pulse, which had been of good volume, becoming rapid and thready. An infusion of normal saline was given intravenously, and two pints of saline were administered before the pulse became of full volume. From this time on, the pulse remained satisfactory. The hernia was repaired by the Wyllys Andrews method, using fine cotton thread sutures.

POST-OPERATIVE PROGRESS.—The patient made a good recovery from the operation, the wound healing by first intention. At the time the anastomosis was done some apprehension was felt at making an end-to-end anastomosis 3 in. from the ileocæcal valve, a site

noted for its poor vascular supply. However, no trouble was experienced from this. The pulse was 126 the next day, and the abdomen was moderately distended. The patient passed a stool spontaneously on the second post-operative day. Seven days after operation, he had bouts of severe colicky abdominal pain associated with a sense of peristalsis, but these ceased in three days. About this time the patient developed a diarrhœa which continued for twenty-one days. On recovery from this he passed one solid stool a day.

An X-ray examination after the administration of a barium meal was made a month after operation. The stomach was almost completely empty in two hours' time, and the barium meal had filled the ascending colon and reached down to the lower end of the descending colon. In three hours' time the meal had left the stomach, jejunum, and upper ileum and was mainly in the colon.

Examination of Stools (Sept. 8): Total fats, 13·6 per cent; Split fat (free fatty acids and soaps), 11·8 per cent; Unsplit fat (neutral fat), 1·8 per cent.

The X-ray examination shows that there is rapid emptying of the stomach and small intestine. Nevertheless, the patient was passing only one solid stool a day, and the analysis of the fat content showed that the functions of absorption were normal. The resection of 5 ft. of ileum had no apparent ill effect on the patient and he left hospital a month after operation feeling fit and well.

A CASE OF REVERSED ROTATION OF THE MID-GUT AND INTESTINAL OBSTRUCTION

By MAXWELL ELLIS, Wing Commander, R.A.F.V.R.

Congenital abnormalities resulting in unusual positions of the intestines are not uncommon, and a considerable amount of information has been accumulated about the causative dynamics as well as the clinical aftermath. Dott's (1923) description of the embryology is the classical exposition, and his beautiful illustrations clarify any faint obscurities that may be found in the text. The most rare of these abnormalities is reversed rotation of the mid-gut where the caudal portion of the loop of gut in the umbilical cord returns first into the general abdominal cavity and then rotates clockwise through 90°. The transverse colon comes to lie behind the superior mesenteric vessels, and thus behind the mesentery carrying the small intestine. In addition, the mesentery of the cæcum and ascending colon often fails to adhere to the posterior abdominal wall, and these organs then acquire an undue mobility. It is probable that this condition nearly always results in clinical mischief, as clinicians are responsible for the majority of the recorded cases. Gardner and Hart (1934) and Truesdale (1935) have collected 19 cases, and I have found 7 others in the literature (Donald, 1927; King, 1927; Doyle, 1937; Grant, 1940; Jessop, 1940; Holman, 1940; and Rose, 1941). Intestinal obstruction is the resulting lesion, due either to volvulus of the mobile cæcum and ascending colon, or to narrowing of the lumen of the transverse colon in its passage behind the small intestine mesentery. A further case of the latter type has recently been encountered.

CASE REPORT

History.—An airman, aged 29, was admitted to an R.A.F. Station hospital on Oct. 7, 1942, with a history of an attack of diarrhœa seven days previously lasting for one night, together with abdominal pain. The pain persisted and he had been constipated for the four days before admission. He vomited on a number of occasions. A mild epidemic of enteritis was occurring at that time in the neighbourhood, and he was admitted to the Infectious Diseases Hospital with a tentative diagnosis of infective enteritis. However, the constipation was not relieved, although he passed a little flatus, but his general condition remained good and free from any anxiety until Oct. 12, when he began to appear somewhat dehydrated. A soap enema produced a small amount of fæces, and he spent a good night, but on the following day the abdomen was slightly distended and a little tender on deep palpation. Constipation was absolute. That night he complained of a good deal of pain, and vomited some brownish fluid. When I saw him on Oct. 14 his tongue was dry and coated, and there was a fæcal odour in his breath—the abdomen was very distended and tender all over. There was no visible peristalsis. His pulse-rate, which had been 80 to 90, was now 112, but the temperature, which had been swinging from 98° to 99°, had not risen. On searching questioning, the patient recalled that he had suffered from a number of similar, but much less acute, attacks in the past. None had lasted more than a day or two. A diagnosis of intestinal obstruction, probably due to volvulus, was made, and the abdomen was explored forthwith.

At Operation.—A right lower paramedian incision was made. Much free turbid and blood-stained fluid was found in the peritoneal cavity, and there was very great distension of the small gut, cæcum, and ascending colon. The splenic flexure and the remainder of the colon distally were collapsed and pale. The great omentum, the splenic end of the transverse colon, and the stomach were all bound up in adhesions under the spleen. The ascending colon passed upwards deep to the small intestine mesentery at its root and entered the adhesions. The distal ileum, cæcum, and ascending colon were all unusually mobile, and it was at first thought that the condition was a volvulus of the whole of the small intestine and ascending colon. However, an attempt to rotate the bowel into a more normal position was found impossible, and a diagnosis of congenital malformation of the large gut (reversed rotation) was made. A cæcostomy was performed through an oblique stab wound in the right iliac fossa, and the paramedian wound sutured without drainage. Curiously enough, in spite of the handling of the intestines, the pulse-rate at the end of the operation was 104.

PROGRESS.—The immediate result was dramatic. The cæcum drained freely, and during the next afternoon the patient passed a copious liquid motion per rectum. Some consolidation at the left base developed, but this cleared up very quickly and without incident on full doses of sulphathiazole. The cæcostomy continued to drain well, and regular rectal motions were secured by small doses of liquid paraffin. By Oct. 28 the fæces were almost entirely being evacuated by the normal route, and very little drained from the cæcum. On Nov. 4, the patient started getting up, and a fortnight later an attempt was made to delineate the condition radiologically with the co-operation of Sq.-Leader J. Courtney. A barium enema was given which unexpectedly revealed a large redundant loop of colon in the splenic area. A true lateral view showed the transverse colon immediately anterior to the vertebral column. The patient was then made to flex the trunk at the hips, which would shift the transverse colon, if it were normal in position, forwards under the anterior abdominal wall. However, it did not move at all, and loops of small intestine were clearly seen between it and the anterior abdominal wall (*Figs.* 64–66). The barium enema was followed by somewhat unexpected complications. For one thing the barium caused almost complete obstruction, relieved with great difficulty by bowel wash-outs and liquid paraffin, and taking over a week to resolve. A mild form of enteritis then developed and the cæcostomy worked overtime, resulting in much excoriation of the surrounding skin, and all question of a further operation was postponed. But early in February, 1943, operative treatment again became possible.

FIG. 64.—Barium enema showing the redundant loop of colon beginning at the splenic flexure.

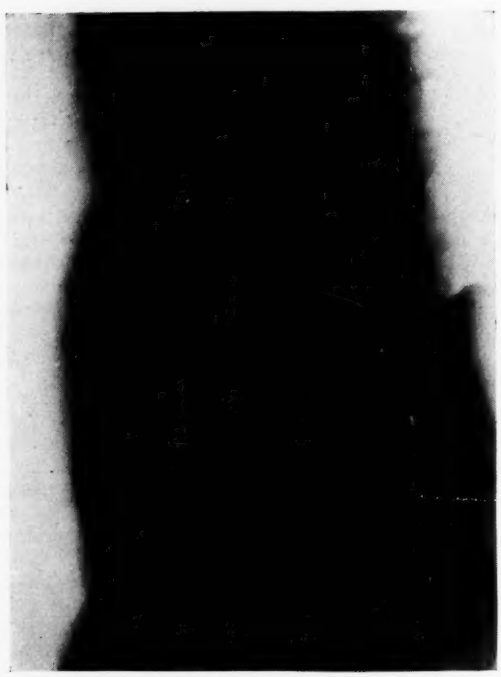

FIG. 65.—Barium enema. True lateral position with the patient erect, showing the transverse colon against the vertebral column.

FIG. 66.—The patient has moved from the position of *Fig.* 65 by flexing the trunk at the hips. Shows how the transverse colon and vertebral column move together, and loops of small intestine between the transverse colon and the anterior abdominal wall.

SECOND OPERATION.—The patient was seen by Air-Commodore Stanford Cade, who explored the abdomen on Feb. 13. Some flimsy adhesions were present as a result of the previous operation, but otherwise the condition was exactly as then found. It was very clearly seen that at the level of the hepatic flexure the transverse colon disappeared into a tunnel behind the mesentery of the small intestine. It would have been quite impossible to excise that part

of the colon lying posterior to the small-intestine mesentery owing to the massive adhesions in the splenic region. It was also difficult to identify with certainty the most distal loop of ileum. Accordingly, the ascending colon immediately distal to the cæcum was anastomosed laterally to the sigmoid colon.

PROGNOSIS.—Again convalescence from the abdominal point of view was quite uneventful, and no chest complications developed. The rectum and cæcum both worked well, and the cæcostomy was closed on March 19. Thereafter the patient had no further bowel symptoms and passed a regular daily motion *per vias naturales*. He was discharged from hospital on April 22 fit and well and back to his normal weight. He was then on a normal diet. It was thought safer, and probably more in the patient's own interests, to discharge him from the R.A.F.

DISCUSSION

Symptoms.—A study of the recorded cases shows that the condition may give rise to no symptoms at all, and may only be discovered in the dissecting room or at operation for some other disease. However, this is rare. Generally acute intestinal obstruction is the presenting clinical picture, although careful inquiry then or subsequently usually discloses either a long history of chronic constipation or the previous occurrence of a number of similar but milder attacks of acute obstruction.

Diagnosis.—It is unlikely that the diagnosis in an acute case could be made with certainty before operation. The nearest attempt would probably be volvulus of some kind, and indeed this would be strictly correct, except that the volvulus is of an irremediable and permanent kind.

Radiography.—Radiography has so far contributed little to the diagnosis of this condition. Rose (1941) has not found a single recorded instance of the discovery of this abnormality during routine investigations. A barium enema examination of his own case revealed a redundancy of the left side of the transverse colon and splenic flexure similar to that shown in the case recorded above. The added criterion of fixity to the posterior abdominal wall of some portion of the transverse colon must be established before the diagnosis can be made, and this can be achieved by the manœuvre described.

Treatment.—In the immediate treatment of acute cases, the majority, radical measures are out of place and their employment is perhaps responsible for the very high mortality. There are two methods of presentation at exploratory laparotomy: (1) Obstruction due entirely to volvulus of the mobile distal ileum, cæcum, and ascending colon; (2) Obstruction of the transverse colon in its tunnel posterior to the superior mesenteric vessels.

In the first group, the volvulus must be untwisted, and a cæcostomy is desirable both as a measure of bowel drainage and rest, and also as a method of eventual cæcopexy to prevent recurrence of the condition. In the second group, cæcostomy is the only rational immediate procedure.

The remote treatment is perhaps slightly more controversial. Although cæcopexy will probably prevent further attempts at volvulus, there is no guarantee that obstruction may not subsequently occur at the root of the small-intestine mesentery. It is, therefore, probably safest to treat all cases alike. Ideally the correct treatment should be excision of the cæcum and ascending colon to the right of the superior mesenteric vessels, retraction of the left portion of the transverse colon out of the mesenteric tunnel, and anastomosis of this to the severed ileum. The dangers both of obstruction and volvulus would then be avoided. However, for various reasons, this may be impracticable, as in the present case. Some form of short-circuit should then be performed, ileo-sigmoidostomy perhaps being the safest, followed by closure of the cæcostomy and cæcopexy.

I wish to thank Air Chief Marshal Sir Harold Whittingham, Director-General of Medical Services, Royal Air Force, for permission to publish this case.

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THE RESULT OF OPERATIVE REPAIR OF SEVERE ACROMIO-CLAVICULAR DISLOCATION

BY A. N. BIRKETT, NOTTINGHAM

THE results of operative attempts to overcome the disabilities of severe injuries are always incalculable when dealing with the skeletal and locomotive systems. This short account describes the result following operation for the repair of the coraco-clavicular and acromio-clavicular ligaments in a soldier.

The man was 29 years of age and suffered a severe initial injury (April 26, 1943), being crushed between two lorries. Presumably the force

compressing him was oblique, so that the right scapula was pushed forwards against the clavicle, which tore adrift from the acromio-clavicular and coraco-clavicular ligaments and the outer end of the clavicle was forced under the trapezius, tearing into and burying itself in the muscle, where it remained trapped. When he attended hospital X-ray examination revealed the position shown in *Fig.* 67. The clinical appearance was that of gross swelling and bruising of the shoulder and supraclavicular region.

FIG. 67.—Radiograph, before operation, showing the extent of the dislocation.

FIG. 68.—Radiograph immediately after repair. Some degree of subluxation is present owing to insufficient tension on the fascia lata strips.

FIG. 69.—Radiograph, fourteen weeks later, showing calcification along the fascial tracts.

FIG. 70.—Radiograph eight months after operation, showing further calcification of the bony link between clavicle and coronoid process.

With most acromio-clavicular dislocations the abnormal mobility allows approximate reposition of the bony fragments by manual manipulation, but in this case the clavicle appeared to be firmly trapped under the muscle and the outer end of the clavicle could not be withdrawn. As the acromio-clavicular dislocation was obviously severe, it was decided to wait the subsidence of the swelling of the soft tissues and then to carry out open reduction and retain the clavicle in position by the use of fascia lata, after the manner of the operation described by Bunnell.

I explored the region (April 30) through an incision over the outer third of the clavicle and the anterior extremity of the acromion process of the scapula. Reduction of the deformity was difficult and the clavicle had to be literally torn out of the trapezius to disimpact it. Reduction of the joint then became easy. A ribbon of fascia lata was passed down through a hole bored in the clavicle lying above the coracoid process. This was passed under the coracoid process and brought out again over the clavicle, down through a second hole close to the acromio-clavicular joint, under this, and out through a third hole in the outer end of the acromion. The two ends of the fascia lata were then pulled tight and sewn together on the top aspect of the clavicle. This system of fascial grafting produced satisfactory fixation of the clavicle, both with regard to its approximation to the coracoid and to the re-alinement of the acromio-clavicular joint. The remains of the coraco-clavicular ligament were brought together to reinforce the fascial strip. The wound was closed and the arm supported by a bandage to take the weight off the newly-inserted fascial graft. Check radiograph of the shoulder (*Fig.* 68) showed that the fascia had not been stretched tight enough to prevent some degree of subluxation.

The clinical course then became uneventful; he overcame the stiffness of the shoulder and made slow but steady progress towards excellent movement and strength of the shoulder, while the clinical appearance gave no suggestion of any tendency to subluxation. Fourteen weeks after the operation he fell on his right shoulder, hurting himself, and was rather frightened lest he should have done further damage. X-ray examination was carried out and on this occasion I was surprised to see that the attempted reinforcement of the ligament had resulted in marked calcification along the fascial tracts, and it appeared that

ossification was in progress (*Fig.* 69). Function of the shoulder, however, did not seem to be greatly impaired. Improvement was steady, and a subsequent radiograph (*Fig.* 70) taken eight months after operation showed further consolidation of the bony link between the clavicle and coracoid processes. At this stage the clinical appearance of the shoulder remained unchanged. He had stability and reasonable strength. There was some restriction of scapula movements and, in consequence, of arm movements, though this restriction was not as marked as one would imagine, and the condition appeared definitely preferable to that of persistent acromio-clavicular dislocation.

A FATAL CASE OF TRAUMATIC THROMBOSIS OF THE INTERNAL CAROTID ARTERY

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Injury to the neck is an occasional cause of damage to the carotid artery, which may be severe enough to be followed by a spreading thrombosis with hemiplegia. An unusual case of traumatic dissecting aneurysm of the left internal carotid artery, followed by massive infarction of the related cerebral hemisphere, is described below. The patient came under the care of a mobile neurosurgical unit stationed at a military hospital in the Middle East, and died 48 hours later, thus affording the opportunity of investigating the mechanism of the lesion at autopsy. The interest of the case lies in the problems of differential diagnosis, and in the pathological findings.

CASE REPORT

History.—On the morning of Aug. 19, 1942, the patient, a signalman aged 31, was walking along a military road, accompanied by a friend, when they were overtaken from behind by a lorry travelling in the same direction. According to the statement of his friend, a piece of loose rope hanging from the side of the lorry wound itself round the patient's neck, threw him to the ground, and then unwound itself without dragging him along. He picked himself up, and, though he felt faint and was suffering from a superficial laceration in the right parietal region, he was able to accompany his friend on foot to the Unit Medical Officer. He was then sent to the nearest reception station, where a single stitch was inserted in the scalp wound. Bruising of the left side of the neck was noted at the reception station, and in view of slight amnesia he was forwarded to a general hospital for observation.

On arrival he gave a consecutive story, but on close questioning admitted that, though he heard the lorry approaching and subsequently remembered picking himself up, he had no recollection of the details of the accident, which he had obtained from his friend. As his injuries appeared to be of a trivial nature, he was detained overnight, but not actually admitted to hospital.

On the following morning (Aug. 20) a routine examination was carried out by the ward medical officer, who noted that his general condition was good. He was alert, rational, and co-operative, and was able to repeat the story given on the previous day. A single stitch was in situ in a small wound in the *right* posterior parietal region. His neck showed superficial abrasions of the throat, more marked on the *left* side, with a swelling in the left sternomastoid, just above the clavicle, which was thought to be a hæmatoma, causing some stiffness on movement. A superficial examination of the central nervous system showed no abnormality.

An hour later, while re-dressing the scalp wound, the sister noticed that the patient did not respond readily when she spoke to him, and twenty minutes later she was recalled because it was noted by other patients that he had flopped over in bed. The sister observed jerky movements of the right arm and leg, and reported to the ward medical officer that he had had a fit. When the medical officer saw the patient fifteen minutes later, he was completely unconscious, could not be roused, and had a complete right flaccid hemiplegia.

Shortly after, he was seen by one of us (G. B. N.). The patient was unconscious but could be roused by the spoken voice. He could open his eyes and mouth when asked, but would not put out his tongue. No attempt at speech was made. On examination his cranial nerves were normal apart from a diminished right corneal reflex and right lower facial weakness. The remainder of his central nervous system showed no abnormality except a complete right flaccid hemiplegia with extensor plantar response. Routine examination of his other systems was clear.

In view of this cerebral catastrophe he was transferred to the Neurosurgical Unit for exploration. Because this followed a head injury and there had been a lucid interval, intracranial bleeding—possibly a middle meningeal hæmorrhage on the left—was suspected.

X-ray examination revealed no fracture of skull or spine.

An exploratory temporal burr hole was made two hours later (G. B. N.). There was no evidence of extradural bleeding, the dura was not tense, and on incising it, normal cerebrospinal fluid escaped. The underlying brain appeared healthy. The left lateral ventricle was tapped and 5 c.c. of clear colourless fluid, not under pressure, were withdrawn, and the wound closed.

The same evening, seven hours later, his unconsciousness had increased to deep coma, the temperature was normal, pulse 40 and irregular, and respirations 20. He had vomited once. The right flaccid hemiplegia

remained unchanged, and he had developed catatonia in the left arm.

On the following morning (Aug. 21) his general condition was worse, his respiration became bubbly, and he died, 48 hours after his accident, and 19 hours after operation.

POST-MORTEM APPEARANCES.—The autopsy was performed by one of us (A. D. M.) with the following findings.

On *external examination*, the body was that of a well-nourished young man. Running round the neck was a reddish band of discoloured skin, 1 in. broad, of parchment-like consistence, resulting from constriction of the throat by the rope. The pressure-mark commenced 2½ in. below the right ear and ran horizontally round the front of the neck for two-thirds of its circumference, crossing the thyroid cartilage and ending at the anterior border of the left trapezius. Below this level the left sternomastoid muscle bulged unnaturally. In the right posterior parietal region was a healing scalp wound 1 in. long. A recent vertical surgical incision, 3 in. long and closed by sutures, was present in the left temporal region.

FIG. 71.—Showing the changes in the first 1½ in. of the internal carotid artery as a result of traumatic thrombosis.

On dissection of the *neck*, some two-thirds of the substance of the left sternomastoid muscle was found to have been ruptured, the retracted fibres forming swellings at its upper and lower ends, leaving a thinned-out strip of muscle at the level of injury. The first 1½ in. of the left internal carotid artery were transformed into a hard bluish, spindle-shaped swelling as a result of traumatic thrombosis (*Fig.* 71). The left common carotid and external carotid arteries were patent. On cutting the thrombosed internal carotid artery longitudinally, the mechanism of the thrombosis was revealed. The main thrombus lay just above the origin of the internal carotid artery, extending upwards for 1½ in. The original lesion was presumably a tearing of the intima and media, with extravasation of blood into the media, raising both intima and media from the outer layers of the vessel wall. As the hæmorrhage increased in size, the lumen of the vessel became narrowed, until finally the rucked-up intima and media completely blocked the lumen in the form of an inverted valve, with the thrombosed blood below it (*Fig.* 72). Following total occlusion, more recent thrombosis occurred above the level of injury, spreading upwards into the petrous and cavernous portions of the vessel to continue into the left middle cerebral artery, resulting in massive infarction of the left cerebral hemisphere.

The *right* internal carotid artery showed a patch of atheroma at the site of compression, 1 in. in length, but the great vessels on this side were free of blood-clot. Both internal and external jugular veins were patent. The larynx, thyroid gland, nerves, and other structures at the level of constriction were intact.

On examination of the *head*, the wound in the right posterior parietal region was seen to be purely superficial. Apart from a burr hole in the left temporal fossa, the skull was intact. The dura mater and venous sinuses were healthy. The spread of thrombosis was found to involve the left half of the circle of Willis and most of the left middle cerebral artery. The clot extended along the first ½ in. of the left anterior cerebral artery, and throughout the left posterior communicating branch. The greater part of the left cerebral hemisphere was softened, but not unduly swollen. An attempt at collateral circulation was observed in the leptomeninges, and superficially the degree of vascularity of the meningeal vessels on each side was the same. On section of the brain, pallor and œdema of the left cerebral hemisphere were noted.

FIG. 72.—Showing the blocking of the lumen, with the thrombosed blood below.

The *thorax* and *abdomen* showed nothing of note.

HISTOLOGY.—

1. *Left Internal Carotid Artery.*—The lesion proved to be in effect a dissecting aneurysm of traumatic origin. The rupture occurred in the outer third of the tunica media, extravasated blood tracking along the plane of fission for the first 1½ in. of the vessel, while the inner two-thirds of the media and the intima retracted into the centre of the vessel, being pushed from below upwards by the blood-flow to form a sort of inverted valve blocking the lumen. Thrombosis occurred below this throughout the length of the denuded area, the clot distending the remaining outer part of the media and adventia to form a spindle-shaped aneurysm. The intima previously lining the affected segment showed well-marked atheromatous changes, obviously of long standing. The underlying media showed no signs of pre-existing disease.

2. *Right Internal Carotid Artery.*—The first inch or so of the vessel showed a moderate degree of atheromatous degeneration of the intima, the media being unaffected.

3. *Brain.*—On the *left* side the meningeal vessels were congested but not thrombosed. The grey matter of the cerebral cortex was grossly œdematous, the œdema causing great distension of the pericellular spaces, each contained nerve-cell being flattened into a crescent against the wall of the space. Most of the nerve-cells were shrunken and degenerate. The supporting neuroglia was teased out into a very open network of fine fibrils. There was a notable lack of cellular infiltration, possibly due to the absence of free blood-flow through the part. Near the surface a few small perivascular hæmorrhages were observed. Many small blood-vessels were largely dilated, with apparently necrotic walls, thus obliterating the Virchow-Robin spaces; but in most of the vessels the lumen appeared to be empty apart from an albuminous fluid, some of which had exuded into the surrounding brain tissue, causing disruption of neuroglia. A few vessels contained small thrombi. In the underlying white matter the myelin sheaths were widely separated by œdema. The internal capsule and basal ganglia showed changes similar to the above. Corresponding

portions of the *right* cerebral hemisphere exhibited œdema but not degeneration.

COMMENT

This case is interesting on account of the bizarre nature of the accident, and instructive because of the problems arising in differential diagnosis. The presence of a head injury, with a lucid interval following a short amnesia, and subsequent development of hemiplegia, naturally suggested an intracranial hæmorrhage. In this case the diagnosis of a left-sided cerebral lesion was particularly clear, in spite of the wound on the opposite side.

It is realized, in the light of the subsequent autopsy, that too great clinical emphasis was laid on the head injury. What was believed to be a hæmatoma in the left sternomastoid was, in fact, the retracted fibres of the torn muscle, a lesion which might have directed attention to the underlying artery.

The mechanism of a dissecting aneurysm is believed to be a rupturing of the inner part of the media, followed by giving way of the intima, thus allowing blood from the vessel to spread in the substance of the media, splitting it up into two layers. It is probable that in this instance the constricting and (more particularly) the tearing force of the rope, which caused rupture of the left sternomastoid, was sufficient to damage the media of the underlying artery. The presence of atheroma at the site of injury is probably coincidental. In the course of thirty subsequent autopsies in men of military age the great vessels were opened as a routine, and in almost every case a variable degree of atheroma was observed at the bifurcation of the common carotid arteries.

SUMMARY

A case is described with a peculiar injury to the neck (trauma caused by a loose rope hanging from a passing vehicle) followed by coma, hemiplegia, and death in 48 hours.

Subsequent autopsy showed that the injury caused a traumatic dissecting aneurysm of the left internal carotid artery, followed by a spreading thrombosis with cerebral infarction.

We have to thank Colonel H. D. F. Brand, Officer Commanding a general hospital, for permission to publish this case. The photographs were taken by Major P. B. Ascroft, former O.C. a Mobile Neurosurgical Unit. Our thanks are also due to Brigadier Hugh Cairns for the interest he has shown in the case.

REVIEWS AND NOTICES OF BOOKS

Fractures of the Jaws and other Facial Bones. By GLENN MAJOR, B.S., A.M., M.S., Ph.D., D.D.S., M.D., F.A.C.S., Pittsburgh. With chapters on Radiographic Technic by LESTER M. J. FREEDMAN, B.S., M.D., and War Aspects of Jaw Fractures by ARTHUR DICK, D.D.S., M.D. 9¾ × 6¾ in. Pp. 446, with 225 illustrations. 1943. London: Henry Kimpton. 37s. 6d. net.

THIS is a comprehensive book covering every aspect of jaw injuries, and it is published at an opportune time when surgeons, both in civil and military practice, require a practical knowledge of fractures of the jaws.

The emergency treatment is well set out and many practical and useful methods are considered in detail. The treatment of shock is given in an up-to-date and sound fashion. The problem of anæsthesia is discussed in detail, and the pros and cons of sodium pentothal are stressed.

The general types of fixation are all described and the importance of interdental wiring is emphasized. Perhaps the best part of the book is devoted to the post-operative care of fractures of the jaws, as the author draws on his vast clinical experience at Pittsburgh.

The chapter on radiographic technique will be found of value to the surgeon who may not be *au fait* with the different positions used to show difficult fractures.

The chapter on War Aspects of Jaw Fractures by Arthur Dick will prove of value at the present time.

The illustrations are numerous and uniformly good.

Emergency Surgery. By HAMILTON BAILEY, F.R.C.S. (Eng.), Surgeon, Royal Northern Hospital, London; etc. Fifth edition. 8⅞ × 5⅞ in. Pp. 969 + viii, with 1039 illustrations, a large number in colour. 1944. Bristol: John Wright & Sons Ltd. 75s. net.

ALTHOUGH the fifth edition has only 25 more pages than the fourth, there are six extra chapters and over 100 more illustrations. It has been extensively revised and made as up-to-date as any book can be by the addition of an appendix containing notes on more recent advances. Full advantage has been taken of the use of colour, not only in the natural illustrations but also in the diagrams, such as those showing the pathway of urinary extravasation. That it has been produced at all is evidence of the determination both of the author and the publishers, for not only was the whole original work destroyed but the new edition was again bombed when nearly ready for publication. Nevertheless, it bears few of the the stigmata of a war production; the margins are a little smaller, but the greatest loss is the ribbon bookmark!

This work has made for itself a place in the library of every practising surgeon; the early demand for a fifth edition only serves to emphasize its utility. There is scarcely any surgical emergency upon which useful guidance is lacking, and whether one agrees with every method suggested or not one can at least be certain of finding sound practical instruction in what to do and when to do it.

Medical Clinics on Bone Diseases. A Text and Atlas. By I. SNAPPER, M.D., formerly Professor of Medicine, Peiping Union Medical College, Peiping, China. $10\frac{7}{8} \times 8\frac{1}{2}$ in. Pp. 225 + ix, with 30 Plates. 1943. New York: Interscience Publishers, Inc. (London: H. K. Lewis & Co. Ltd.). 67s. 6d. net.

OUR knowledge of bone diseases and their pathology has increased enormously during the last quarter of a century. Professor Snapper, who has had vast experience at the Peiping Union Medical College in China, has written and illustrated a most useful book on bone diseases. The book is unique in many ways, for the text is illustrated by some thirty excellent plates which incorporate the X-ray picture and photomicrographs of the disease. This is the only way to teach the pathology of bone diseases. Not only are the common bone diseases described and illustrated, but uncommon conditions such as Recklinghausen's disease, multiple myeloma, Gaucher's disease, lipoid granuloma, osteogenesis imperfecta, and osteomalacia, are all set out in detail and beautifully illustrated.

As a work of reference this book could not be bettered.

Orthopædic Surgery. By WALTER MERCER, M.B., Ch.B., F.R.C.S. (Edin.), F.R.S. (Edin.), Assistant Surgeon, Royal Infirmary, Edinburgh; etc. With a Foreword by Sir John Fraser, Bart., K.C.V.O. Third edition. $8\frac{7}{8} \times 5\frac{5}{8}$ in. Pp. 947 + xi, with 415 illustrations. 1943. London: Edward Arnold & Co. 45s. net.

IN its third edition this well-known special surgical text-book has expanded to nearly a thousand pages. New matter has been added and every chapter has been revised and brought up to date. The work has all the virtues—and some of the weaknesses—of the Edinburgh school of surgical teaching. Nothing—or very little—has been left out. In its form it is the didactic course of lectures *par excellence*—comprehensive, clear-cut, and impersonal. As such, it will for some time to come be the leading text-book of reference in this field of surgery, not only for those reading for the higher surgical diplomas, but also for the practising orthopædic surgeon.

BOOK NOTICES

[*The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest for our readers.*]

The 1943 Year Book of Industrial and Orthopedic Surgery. Edited by CHARLES F. PAINTER, M.D., Orthopedic Surgeon to the Massachusetts Women's Hospital and Beth Israel Hospital, Boston. $7 \times 4\frac{5}{8}$ in. Pp. 440, with 306 illustrations. 1943. Chicago: The Year Book Publishers Inc. $3.00.

An Atlas of Anatomy. By J. C. BOILEAU GRANT, *M.C.*, M.B., Ch.B., F.R.C.S.(Edin.), Professor of Anatomy in the University of Toronto. In two volumes. $11 \times 8\frac{1}{2}$ in. Vol. I, Upper Limb, Abdomen, Perineum, Pelvis, and Lower Limb. Vol. II, Vertebræ and Vertebral Column, Thorax, Head, and Neck. Pp. 390 + xii, with 460 illustrations. 1943. Baltimore: The Williams & Wilkins Co. (London: Baillière, Tindall & Cox). The set, 55s. net.

Demonstrations of Physical Signs in Clinical Surgery. By HAMILTON BAILEY, F.R.C.S. (Eng.), Surgeon, Royal Northern Hospital, etc. Ninth edition. $8\frac{3}{4} \times 5\frac{1}{2}$ in. Pp. 351 + viii, with 492 illustrations, a number of which are in colour. 1944. Bristol: John Wright & Sons Ltd. 25s. net.

Structure and Function as seen in the Foot. By FREDERIC WOOD JONES, D.Sc., F.R.S., F.R.C.S., Professor of Anatomy, University of Manchester. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 329 + iv, with 150 illustrations. 1944. London: Baillière, Tindall & Cox. 25s. net.

The Hospital Care of the Surgical Patient. A Surgeon's Handbook. By GEORGE CRILE, jun., M.D., Surgeon, Cleveland Clinic, and FRANKLIN L. SHIVELY, jun., M.D., Assistant Surgeon, Cleveland Clinic. With a Foreword by EVARTS A. GRAHAM. $8\frac{1}{4} \times 5\frac{1}{2}$ in. Pp. 184 + xv, with 21 illustrations. 1943. Springfield, Ill.: Charles C. Thomas (London: Baillière, Tindall & Cox) 14s. net.

The Diseases of the Endocrine Glands. By HERMANN ZONDEK, M.D. (Berlin), Director of the Medical Division, Bikur Cholim Hospital, Jerusalem. Fourth (Second English) edition. Translated by CARL PRAUSNITZ GILES, M.D. (Breslau), M.R.C.S. (Eng.), L.R.C.P. (Lond.). $9 \times 5\frac{3}{4}$ in. Pp. 496 + viii, with 180 illustrations. 1944. London: Edward Arnold & Co. 40s. net.

Vascular Responses in the Extremities of Man in Health and Disease. By DAVID I. ABRAMSON, M.D., F.A.C.P. 9 × 6 in. Pp. 412 + x, with 59 illustrations. 1944. Chicago, Ill.: The University of Chicago Press (London: Cambridge University Press). 30s. net.

Regional Analgesia. By H. W. L. MOLESWORTH, F.R.C.S. Eng., Senior Surgeon, Royal Victoria Hospital, Folkestone; etc. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 90 + viii, with 42 illustrations. 1942. London: H. K. Lewis & Co., Ltd. 8s. 6d. net.

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Special Issue

PENICILLIN IN WARFARE

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THE
BRITISH JOURNAL OF SURGERY

VOL. XXXII SPECIAL PENICILLIN ISSUE

EDITORIAL

PENICILLIN

PENICILLIN is an antibacterial agent of extraordinary potency and is now available in increasing amounts for the treatment of war wounds.

In publishing this compendium the aim of the BRITISH JOURNAL OF SURGERY has been to provide an authoritative account of the properties of penicillin, the principles of its application to wounds, and the laboratory methods by which its use should be controlled.

The actual clinical experiences in the treatment of recent war wounds in the field with penicillin, while already considerable, are submitted herein as being for the most part of a preliminary character.

The compendium is not comprehensive, nor does it provide precise directives on the use of penicillin. These are issued by the various medical services, and, in the present state of rapid development of the techniques in the use of penicillin, frequent changes of instruction may be expected.

All references to previous published work on penicillin are set out in a comprehensive bibliography at the end of the fasciculus.

FOREWORD

ARMY PROGRESS WITH PENICILLIN

By Major-General L. T. POOLE, D.S.O., M.C., K.H.P.
DIRECTOR OF PATHOLOGY, WAR OFFICE

Penicillin, first described by Fleming (1929), was introduced to the Army in April, 1942, when, at a meeting of the War Wounds Committee of the Medical Research Council, Professor Florey (now Sir Howard Florey) offered the War Office a small quantity of the drug that had been prepared in the Sir William Dunn School of Pathology at Oxford. He foresaw the possibilities of its use in war surgery and was anxious that it should be tried on our wounded in the Middle East. The strength of the first batches that the Army received varied from 30 to 40 Oxford units per mg. This is in marked contrast to the potency of some of the present-day preparations, which have a strength of about 1600 units per mg.; the difference clearly indicates the progress made in the manufacture of the drug during this very short period.

At that time communications with the Middle East were most uncertain; but the difficulties were overcome and the penicillin sent out by air. Results were anxiously awaited. In due course an interim report was received, and in November, 1942, Professor Florey wrote in reply: "I have heard that you have received some penicillin from me in good order and that it has been used on at least one case with some encouraging results." That was the state of our knowledge less than two years ago. The full report from the Middle East (Pulvertaft, 1943) dealt with the treatment of 15 cases and confirmed the worth of penicillin in the control of wound sepsis. The success of this trial marked the first milestone of our progress towards the use of penicillin in battle casualties; further deliveries of the drug were eagerly sought. But at this time supplies were very limited.

In the meantime the North African front had been well established and transport was no longer a difficulty. The War Office, therefore, sent a small team of workers to North Africa to determine how penicillin could best be employed in the field. The Penicillin Team, as it was called, consisted of Lieut.-Colonel Ian Fraser, R.A.M.C., surgeon, and Major Scott Thomson, R.A.M.C., pathologist, together with one technician. They set sail for Algiers with 10 million units in May, 1943. Because active operations had ended before they arrived, their first investigation was carried out on septic wounds that in many cases were several weeks old. Professor Florey proceeded to North Africa to review the position and it soon became clear both to him and to the team that, in the treatment of battle casualties, the real place for penicillin was in the early stages of a wound before chronic sepsis had developed.

Our assault on Sicily was impending. At that time I was in North Africa and took the opportunity to discuss with the D.M.S., Major-General Sir Ernest Cowell, our future policy in the use of penicillin and our plans for investigation during the forthcoming battles. As with all research in the field, many difficulties had to be resolved, but this was done through the willing co-operation of the D.M.S. and his staff, both administrative and technical. Before the assault began, Brigadier Hugh Cairns joined the investigators and the results of their work are told in their preliminary report to the War Office and the Medical Research Council that was published by the War Office in October, 1943.*

Publication of this historic document marked the second milestone of progress towards establishing penicillin in the treatment of war wounds. It was a preliminary report, quickly assembled from the contributions of many workers and hurried through the press. It set forth many lessons, learned in a very short time; these had to be made widely and quickly known so that the use of penicillin could be extended. This report made it clear that penicillin had an important place in the treatment of war wounds; fundamental data were set out for study, some guidance on dosage was given, and it was made clear that, with penicillin, an important saving in manpower could be effected by reducing the overall stay of wounded in hospital. It was also evident that many soldiers could quickly be returned to the line by treatment of other war diseases that respond to penicillin.

The written word was reinforced by lectures and demonstrations. The War Office organized courses of penicillin instruction for nearly 200 pathologists and over 500 clinicians at the Royal Herbert Hospital, Woolwich. As time went on others learned of these courses and naval officers, civilians, and members of allied forces were also instructed. Professor Florey's film of Penicillin

* The following surgeons and bacteriologists contributed to the report: Lieut.-Colonel A. L. d'Abreu, Lieut.-Colonel E. L. Button, Lieut.-Colonel I. Fraser, Lieut.-Colonel J. S. Jeffrey, Lieut.-Colonel D. W. Jolly, Major P. Clarkson, Major K. C. Eden, Major W. E. Hamilton, Major J. D. MacLennan, Major W. H. D. Priest, Major J. Shoreston, Major Scott Thomson, Major H. L. de Waal, Captain A. Pirie, Captain G. K. Tutton.

in North Africa was shown and altogether as much as possible was done to ensure that, when penicillin was freely available, medical officers would know how it should be used.

In the light of knowledge and experience, fresh terms of reference of the Penicillin Team were drawn up, putting into effect the recommendations of the Preliminary Report. At this time Lieut.-Colonel J. S. Jeffrey, R.A.M.C., took over the duties of Surgical Penicillin Officer from Lieut.-Colonel Ian Fraser, R.A.M.C., who was invalided home. Lieut.-Colonel Fraser had not only carried out pioneer research but had also displayed great heroism in the field, for which he was awarded the D.S.O.

The early stages of the next phase were hampered by slow delivery of supplies and by the fact that penicillin was dispensed in powder form, either as the sodium or calcium salt, and issued in rather large screw-cap bottles. The amount of penicillin relative to the total weight of the glass container was disproportionately small. As a result packages of penicillin were of undue bulk, and there was great difficulty in sending adequate quantities by air transport to the workers in field. For the rapid and regular dispatch of available penicillin to the Mediterranean theatre, it became clear that the weight and bulk of packing would have to be reduced. Guidance was sought from Dr. J. W. Trevan, of the Wellcome Physiological Research Laboratories, who immediately suggested tableting the penicillin and quickly produced sample packings that were obviously very suitable. From the Army point of view this was a great achievement; for tableting not only solved the problems of transport but also abolished many of the difficulties of dispensing in the field. Slowly but steadily the supply position improved until, from our own and American resources, we were regularly able to dispatch 20 million units a day by air mail to the Italian theatre of operations. Therefore, the third "Penicillin Milestone" was passed when we reached the point where supplies for the Services were enough to allow of extended trials. And the next chapter in the unfolding history of penicillin may be read within. Here is set forth in detail something of what penicillin has already done for the soldier.

Work in the Central Mediterranean Force from December, 1943, to May, 1944, gave results that, in general, fully substantiate the findings in the Preliminary Report. During this period all surgeons experienced in the use of penicillin emphasized most strongly how important it was for everyone to realize that the administration of this drug in no way diminished the need for adequate and early definitive surgery. Greater experience in the field will probably show that neglect of this fundamental principle is the main reason for those failures in the treatment of battle casualties that cannot be entirely avoided. It is only by appreciating the basic importance of careful surgical technique that the value of penicillin as an adjuvant to war surgery can be correctly assessed.

PRACTICAL APPLICATION

Employment of penicillin in the most forward surgical units as a prophylactic against wound sepsis emerges as perhaps the greatest application of the lessons learned from work described here. Under battle conditions, a long interval must sometimes elapse before definitive surgery can be undertaken. Penicillin can be used to bridge this gap and delay, modify, or even prevent, the development of sepsis.

This prophylactic use of penicillin is of special value to wounded among airborne troops; these formations, by their special role in battle, present new problems to military medical men because there is often some delay before the main force joins up and wounded can be evacuated in the usual way.

Along the highway of penicillin progress another milestone now comes in sight—extended routine use of the drug. On this next stage of the journey we shall seek corroboration of the various findings already reported and engage in new investigations that will derive from what has already been achieved. Important questions still challenge us. To answer these there will have to be close association of chemists, pathologists, and clinicians. Much useful and friendly collaboration has characterized the Army's work with penicillin. If this spirit continues and extends, a true and balanced picture of the power and limitations of penicillin will soon be presented to the world.

THE PRINCIPLES OF PENICILLIN TREATMENT

By H. W. FLOREY and M. A. JENNINGS
FROM THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY, OXFORD

THE present great interest in the properties and therapeutic possibilities of penicillin dates from the demonstration in 1940 that it belongs to that rare class of drug—the true chemotherapeutic agent. Fleming discovered in 1929, in a series of observations which have now been frequently described, that the mould, *Penicillium notatum*, produced in the liquid on which it was grown a substance that inhibited the growth of many pathogenic organisms. It was not, however, until a stable extract of the active principle was obtained in 1940 that its somewhat astonishing properties were revealed (Chain et al., 1940; Abraham et al., 1941).

For those who wish to use the new drug with intelligence and understanding it is essential to be familiar with its properties, both chemical and biological. This may be true of many drugs, but in this case it is particularly so, since the drug is delicate and there are many pitfalls in its use. The clinical exploitation of the drug now being so actively pursued, and the experimental findings of the laboratory, are so intimately linked together that it is no picturesque overstatement, but a matter of fact and experience, to say that success in the one is dependent on a lively appreciation of the facts revealed by the other. It is the purpose of this article to set out briefly these fundamental experimental data and to show how they determine the conditions of clinical use.

PROPERTIES OF THE DRUG; STABILITY; DISPENSING

Penicillin can at present only be obtained as a metabolic product synthesized by the mould *Penicillium notatum*. It is extracted from the fluid culture on which the mould has grown by transfer between solvents and other chemical manipulations. When partial purification and great concentration have been achieved the product is dried *in vacuo*, producing a golden powder which is suitable for all clinical purposes. This powder is not penicillin in the strict sense of the word since it contains, as a rule, only from 10 to 30 per cent of the active substance, the rest being made up of impurities which are fortunately but little more toxic than penicillin itself.

Penicillin is an acid, but in the acid form it breaks down very quickly, losing its activity, so that it must always be handled in the form of one of its salts, which under appropriate conditions are stable. At present the calcium and sodium salts are supplied for clinical use and there is nothing to choose between them as regards efficacy. It was at one time thought that the calcium salt had a more damaging effect on the tissues than the sodium salt (H. W. Florey and Jennings, 1942) but this was almost certainly due to impurities, as others have found purer samples to be quite suitable for parenteral use (Herrell and Nichols, 1943; Györgi and Elmes, 1944; other so far unpublished work) and it is very widely used for local application. It has the great practical advantage of being less hygroscopic than the sodium salt and therefore easier to handle and less liable to deterioration.

Even in the form of its salts penicillin is more unstable, and so more subject to loss of activity, than other drugs commonly handled in clinical use. It is destroyed by acid and alkali, by the heavy metals, by alcohols, and by oxidizing agents. As most of the common antiseptic solutions contain some constituent falling into one or other of these categories it is obvious that the penicillin must be used alone, and that before its application wounds should be cleaned only by soap and water or Cetavlon. Penicillin loses activity when heated above body temperature and many specimens are destroyed by boiling; so preparations should always be kept in the refrigerator. Unexplained loss of activity sometimes occurs, perhaps due to impurities in the particular batch and such losses again are minimized by storing in the cold.

Penicillin is also rapidly destroyed by penicillinase, an enzyme contained in, or secreted by, many common airborne bacteria such as members of the coliform and subtilis-mesentericus groups (Abraham and Chain, 1940; Harper, 1943; Duthie, 1944); so for this reason, as well as the possibility of contamination by insensitive pathogens, it is necessary to use sterile instruments and vessels in dispensing, to dilute with sterile cream, powder, or water, and so on. If any contaminant should by accident be present, storage in the cold again diminishes loss.

Solutions should, in general, only be made up on the day of use; if storage is imperative it should be in the refrigerator and for as short a time as possible. Creams may be stored in the refrigerator for a short time, but should not be frozen. Another paper in this number (Garrod and Heatley, 1944) sets out the methods for assaying the activity of penicillin preparations.

Bearing in mind that organisms such as proteus and *Ps. pyocyanea* are not inhibited by penicillin, full aseptic precautions should be taken when penicillin is injected or applied locally.

ANTIBACTERIAL ACTION

Penicillin is the most powerful antibacterial agent which has yet been brought into clinical use, and this, together with its somewhat incongruous origin from a green mould,

has cast a ' magic ' aura around it in the public and even in the medical mind. But its properties are well understood and its powers and limitations can be set out quite simply.

Potency.—Pure penicillin is likely to remain for a long time a chemical curiosity, but its antibacterial capacity is known; it will completely inhibit the growth of the most sensitive organisms, as the gonococcus and staphylococcus, when diluted at least 1 : 50,000,000. The powders now issued for clinical use will inhibit at dilutions from 1 : 5,000,000 to 1 : 15,000,000, and one may expect the quality of clinical penicillin to improve.

Mechanism.—Penicillin was readily shown experimentally to be bacteriostatic and not bactericidal by the fact that suspensions of bacteria continued to take up oxygen at the normal rate even in the presence of high concentrations of penicillin (Abraham et al., 1941)—concentrations very much greater than those likely to be reached in the body tissues. Morphological studies suggest that penicillin, without killing the bacteria, interrupts cell division (Gardner, 1940). Since it remains at the site of application for at the most a few hours, the hope of clearing an infection with a single dose is seldom if ever likely to be realized. As soon as the influence of the drug is removed the bacteria are able to resume multiplication. The good effects of penicillin depend on simultaneous action by the leucocytes and other defence mechanisms of the body, which deal with the bacteria while multiplication is held in check by the penicillin. A combined operation of this sort will usually take several days to complete in any but the most trivial infections. *Penicillin must be kept continuously in contact with all infected tissues until the natural body defences have had time to deal with the infection.* To obtain these conditions by local application of the drug special and sometimes unorthodox surgical manœuvres may be called for.

Effect of Body Fluids.—It was a simple matter to demonstrate in the laboratory that the antibacterial action of penicillin was not significantly impaired by serum, blood, pus, or tissue autolysates (Abraham et al., 1941). It follows that no hesitation need arise in using it on even the most purulent lesions. In this, as also in the fact that penicillin is little affected by the number of organisms present, a sharp contrast with the sulphonamides is seen.

Sensitive and Resistant Bacteria.—The differentiation of pathogenic bacteria into those that are relatively sensitive and insensitive to penicillin, which was made *in vitro* (Fleming, 1929; Abraham et al., 1941), has been fully supported by clinical experience. It is useless to attempt treatment where the infection is caused by an insensitive organism. But in mixed infections elimination of the sensitive species, even if other bacteria remain, may be of great profit.

The grouping of the principal pathogens is shown below. In general, Gram-positive organisms and the Gram-negative cocci are sensitive, and the Gram-negative bacilli insensitive, but some species show strain variation. Naturally resistant staphylococci are occasionally encountered (Scott Thomson, 1944; Spink et al., 1944, a) and the *Str. viridans* group varies considerably. No naturally resistant strain of *Str. pyogenes* has yet been reported.

Organisms Sensitive to Penicillin :—
- *N. gonorrhœæ*
- *N. meningitidis*
- *Staph. albus* and *aureus* (occasional insensitive strain)
- *Str. pyogenes*
- *Str. viridans* (most of the pathogenic strains are sensitive)
- *Str. pneumoniæ*
- *Cl. welchii*
- *Cl. œdematiens*
- *Cl. septique*
- *B. anthracis*
- *C. diphtheriæ*
- *Trep. pallidum*
- *Trep. recurrentis*
- *Leptospira icterohæmorrhagiæ* (probably sensitive though variation)
- Virus of ornithosis and psittacosis
- Virus of lymphogranuloma inguinale

Moderately Sensitive :—
- *Vibrio El Tor*
- *S. gaertneri*

Insensitive :—
- *Ps. pyocyanea*
- *Proteus*
- *B. coli*
- *B. typhosus* and *paratyphosus*
- *Str. fæcalis* and some other strains of *Str. viridans*
- Occasional strains of *Staphylococcus*
- *Listeria*

As with other antibacterial drugs, resistance can be built up *in vitro* or *in vivo* in animals by doses which are not large enough to prevent growth completely (Abraham et al., 1941; McKee and Houck, 1943, a, b), but in clinical practice, according to the data at present available, this is fortunately not common (Rammelkamp and Maxon, 1942; M. E. Florey and H. W. Florey, 1943; Dawson and Hobby, 1944). However, it is advisable on all grounds that a fully bacteriostatic dose should be given from the beginning. The mechanisms of resistance to penicillin and to the sulphonamides are different, since sulphonamide-resistant strains are sensitive to penicillin (McKee and Rake, 1942, b; Herrell, Cook, and Thompson, 1943; Cohn and Seijo, 1944) and the reverse has also been shown (Schmidt and Sesler, 1943; Spink et al., 1944, a, b).

ABSORPTION AND EXCRETION

Before a dose of penicillin was ever given to man it had been possible to work out in animals the biological properties which were to govern its clinical use (Abraham et al., 1941). It had

been shown to be rapidly absorbed from subcutaneous tissue and muscle and to pass thence into the blood-stream, where it could be detected in antibacterial concentration. It was excreted rapidly and in high concentration in the urine (for instance, in one cat 50 per cent of the dose was excreted in the urine in the 5 hours after intravenous injection and higher yields were obtained in man) and was found in the bile and saliva, but not in the tears or pancreatic juice. It could not be detected in the cerebrospinal fluid. Clinical experience has fully confirmed these observations (M. E. Florey and H. W. Florey, 1943; Blake and Craige, 1943; Herrell, 1943, 1944; Lyons, 1943; Mahoney, Arnold, and Harris, 1943; Keefer et al., 1943; Bennett, 1944; Dawson and Hobby, 1944, and others). As expected, infections of the meninges could not be effectively treated by systemic administration, and intrathecal administration was necessary to produce a bacteriostatic concentration in the cerebrospinal fluid (Fleming, 1943; Cairns et al., 1944; Pilcher and Meacham, 1943). Similarly, the pleura and serous membranes of the joints are relatively impermeable to penicillin (Rammelkamp and Keefer, 1943, b), so that infections in these sites are best treated by local application.

In a series of studies on man Keefer and his associates have confirmed and amplified the facts about the fate of penicillin in the body (Rammelkamp and Keefer, 1943, a, b; Rammelkamp and Bradley, 1943; Rammelkamp and Helm, 1943, a, b). Von Sallmann and Meyer (1944) have studied its penetration into the eye. Though it is absorbed from the intestine, administration by mouth or by rectum was from the first seen to be unsuitable, since the acid of the stomach and the bacteria of the large intestine would be expected to inactivate the penicillin before it could be absorbed. This has been confirmed by Rammelkamp and Keefer (1943, b) and Rammelkamp and Helm (1943, b). Some trials with enteric capsules and the duodenal tube were early abandoned because of the uncertainty of these methods (Abraham et al., 1941; M. E. Florey and H. W. Florey, 1943), and they are unlikely to be resumed while penicillin remains a rare and valuable drug. It is possible that even were it introduced directly into the small intestine, considerable destruction would occur, so that much larger doses would have to be used than are efficacious by injection methods.

METHODS OF ADMINISTRATION AND DOSAGE

The rapid absorption and elimination of penicillin, whether after injection or from a wound surface, dictate that relatively large doses shall be given and shall be frequently repeated.

General Administration.—For systemic administration intramuscular or subcutaneous injection is usually used. Little is gained by intravenous injection, as after intramuscular injection maximum concentration is reached in the blood within 15 minutes. Absorption from the subcutaneous tissues is somewhat slower (Rammelkamp and Keefer, 1943, b). Excretion in the urine begins as soon as the penicillin reaches the blood-stream. In the 4th hour after a dose of 15,000 units a bacteriostatic concentration as a rule no longer exists in the blood, so that the dose should be repeated 3-hourly. Excretion is so rapid that probably no advantage is to be gained by increasing the single dose above 15,000 units (Rammelkamp and Keefer, 1943, b), the size originally established as generally effective (M. E. Florey and H. W. Florey, 1943).* The same total dose may be given in a continuous intravenous drip or, as recently shown, a continuous intramuscular drip may be a very convenient method of administration (Morgan et al., 1944). Bloomfield et al. (1944) have used continuous subcutaneous infusion. Herrell (1944) has described good results by intravenous drip giving only 40,000 units every 24 hours, but these small doses cannot be recommended for use at present.

Local Administration.—The same general principles hold good for local as for systemic use—that is to say, a continuous concentration of the drug must be maintained in contact with all infected tissues until the infection has been dealt with by the cellular and humoral defences. To do this may call for some ingenuity both from the surgeon and dispenser. Every infected portion of tissue must be made accessible to the penicillin. Further, sloughs and sequestra should be completely removed as, though the penicillin will diffuse through them in time, leucocytes and tissue fluids will not effectively penetrate to remove the bacteria. Such dead tissue has repeatedly been found to form a focus from which the infection restarts (Robertson, 1944; Mowlem, 1944). Healing can be greatly hastened by early closure of a wound and instillation of penicillin solution 12-hourly through indwelling fine rubber tubes. This was successfully done in the first place in mastoidectomy wounds (M. E. Florey and H. W. Florey, 1943) and has since been done with war wounds (H. W. Florey and Cairns, 1943), and the principle has been applied to chronic sinuses (M. E. Florey and H. W. Florey, 1943) and osteomyelitis (Mowlem, 1944). Abscesses may be treated by aspirating the pus and injecting penicillin through a needle (M. E. Florey and Williams, 1944; Fraser, 1944). Penicillin powder has also a considerable place in the local treatment of wounds (Jeffrey, 1944, a; Mason Brown, 1944). Open infected wound and burn surfaces can usually be rapidly cleared of streptococci and staphylococci by a few days' application of penicillin in a suitable form (Clark et al., 1943; Bodenham, 1943).

* Some advantage may be gained in fresh wounds by larger doses, as the drug may escape in the serum in higher concentration than with small doses and thus have an increased local action.

As has been shown, the cerebrospinal space and the pleural and probably the joint cavities present a special problem in treatment, as penicillin passes but slowly between these cavities and the blood-stream. In meningitis, while systemic treatment is of little use except to prevent or check general invasion in the early stages (though there is evidence that some small amount of penicillin passes through the meninges when they are inflamed), intrathecal injection by the lumbar or ventricular route is most effective, as a bacteriostatic concentration is usually maintained in the cerebrospinal fluid for at least 24 hours (Fleming, 1943; Rammelkamp and Keefer, 1943, a; Cairns et al., 1944). Treatment once daily or even less frequently is sufficient. Similar conditions apply in the treatment of infections in the pleural and joint cavities (Keefer et al., 1943; Dawson and Hobby, 1944; d'Abreu, 1944; Nicholson and Stevenson, 1944).

Infections of the eye (Abraham et al., 1941; M. E. Florey and H. W. Florey, 1943; Robson and Scott, 1943, a, b; Von Sallmann, 1943, 1944; Cashell, 1944) and of the skin (Roxburgh et al., 1944) also offer obvious fields for local application.

The principal preparations for local use are :—

1. *Powder*.—Dry penicillin is diluted with sulphanilamide or sulphathiazole powder (these diluents are less injurious to the tissues than other powders) to give a concentration of from 1000 to 5000 units per gramme. This powder can be blown with an insufflator on to raw surfaces or into wounds, but is only of real use on relatively dry wounds, as blood or exudate rapidly wash it away. Application should be repeated every 24 hours.

2. *Creams*.—Dry penicillin can be incorporated in a cream to a strength of 250 units or more per gramme by mixing with either lanette wax SX 12 parts, arachis oil 25 parts, and water 55 parts, or simply with 30 per cent lanette wax in water. Either makes an excellent dressing for surface or deeper wounds and need not be renewed more often than every 24 or sometimes every 48 hours.

3. *Solutions*.—These may be made up in sterile water or saline at 250 units or more per c.c. and are suitable for instilling through tubes into wounds which have been sutured or injecting by needle into abscess cavities. Solutions of a strength of 1000 to 2000 units per c.c. are suitable for injecting into the cerebrospinal, pleural, and joint cavities or for 2-hourly use as eye drops.

As with general administration, local application must be often repeated. One or two applications cannot be expected to remove the organisms from an established infection.

TOXICITY AND REACTIONS

The early work on penicillin showed it to be remarkably non-toxic to the body tissues (Abraham et al., 1941). Cells in tissue culture and leucocytes would tolerate concentrations hundreds of times greater than those required for bacteriostasis and repeated injection into animals revealed no significant effect on any of the special organs. It was therefore with confidence that the first doses were given to man and clinical experience has entirely supported this confidence. No sign of damage to any organ such as the kidney or bone-marrow has ever been seen. A rise in blood-urea is sometimes reported (M. E. Florey and H. W. Florey, 1943; Lyons, 1943), but in the absence of albuminuria or any other sign of renal damage this rise may reasonably be associated with the unusually rapid disposal of the products of inflammation which the liver and other organs are called on to make.

It was shown by H. W. Florey and Jennings (1942) that with increasing purity the already low toxicity of penicillin preparations fell still further and it is almost certain that such clinical reactions as are seen are due to the impurities which are present in all preparations. As material of increasing purity comes into clinical use workers lay diminishing emphasis on toxic reactions.

1. Thrombophlebitis near the site of injection may develop after a few days of continuous intravenous treatment, but is not often seen after intermittent intravenous injections. No serious results have been reported but a change to another limb or another route of administration is indicated.

2. Generalized urticaria may also occur. Lyons (1943) quotes an incidence of 5·7 per cent in 209 cases, but this figure is higher than that of some other workers. Rarely fever, joint pains, and cramps accompany the urticaria, but the condition is usually mild. There is no evidence of increased sensitivity (penicillin preparations do not contain protein) and treatment may be continued and further courses safely given.

3. A pyrogenic substance is present in crude penicillin. It is usually removed in the course of purification but enough sometimes remains to cause a rigor after intravenous administration. If the same material is injected intramuscularly there is usually little or no temperature disturbance. Before finally implicating the batch of penicillin the water or saline in which it was given should be proved to be free of pyrogen.

4. Pain, usually slight or moderate, is common after subcutaneous or intramuscular injection. Occasionally it is severe enough to make a prolonged course of 3-hourly injections very wearing to a patient who is seriously ill. There may be an indication in such a case for a change to the intravenous route or to continuous slow intramuscular injection. Workers have reported that mixture of procaine with the penicillin to a final concentration of ½ to 1 per cent of the procaine (no other anæsthetic is at present known to be suitable) overcomes the difficulty where the pain is severe enough to be a serious problem, but this is not necessary as a routine measure.

5. Cairns et al. (1944) reported that certain batches of penicillin provoked reactions when

injected into the ventricles or lumbar subarachnoid space. One sample, for instance, produced in 3 subjects a sterile meningitis which lasted 48 hours. Another sample produced more serious effects. In the absence so far of an efficient animal test each new batch of penicillin for intrathecal injection should be used cautiously at first.

ASSESSMENT OF PROGRESS AND DURATION OF TREATMENT

Any discussion of penicillin has failed in its purpose if it has not brought home the idea that this new drug, exacting to handle and unstable though it may be, inhibits all sensitive bacteria to such good effect that the body has a good chance of removing them with a speed and completeness rarely achieved hitherto. Progress and cure are most readily assessed by following the elimination of the infecting organisms from day to day, as in the daily fall of the quantitative blood-culture in septicæmia and the rapid elimination of streptococci from the surface of a burn. The co-operation of the bacteriologist is essential in order to use the drug to the best advantage.

In the *systemic treatment* of early or localized infections, such as may be met with in recent war wounds, a course lasting 3 to 5 days may be enough. For a general or a severe local infection treatment should be continued for at least 2 to 5 days after the infecting organism can no longer be found by bacteriological methods. In a condition such as staphylococcal septicæmia the total period of treatment is seldom less than 10 days and may be much more. Loewe et al. (1944) were able to effect an apparent cure in subacute bacterial endocarditis only after continuous treatment for from 2 to 4 weeks; after shorter periods the streptococcus reappeared in the blood in a few days (in this series the penicillin was given in conjunction with heparin). Acute gonorrhœa, on the other hand, appears to be cured in most cases by a course lasting 24 to 48 hours or even less (Mahoney, Ferguson et al., 1943; Cohn et al., 1944). The general condition of the patient is a good guide to progress. Spirits and appetite improve within a day or two in all but the most serious infections and local pain and swelling are relieved. The temperature falls by lysis and is sometimes maintained for days, only coming back to normal at about the time penicillin is discontinued, or even later. In patients with serious sepsis or toxæmia it is impressive to watch the red and white cell-counts. Even without transfusion the red count begins to rise, perhaps within the first week, and the white count moves towards normal, whether it was previously high because of the sepsis or low from depression of the function of the bone-marrow by bacterial toxins or sulphonamides (M. E. Florey and H. W. Florey, 1943; Lyons, 1943).

In *local treatment* pain is very quickly relieved and swelling disappears early. Again the bacteriological reports are most valuable in assessing progress (M. E. Florey and Williams, 1944).

Special mention should be made of the radiological appearances in bone infections treated either locally or systemically. During the course of penicillin rapidly advancing rarefaction is seen and is most alarming to those unfamiliar with the phenomenon. It has proved never to be a sign of progressive destruction and apparently indicates the quick absorption of inflammatory products. Left alone the bone regenerates, without sequestrum formation (M. E. Florey and H. W. Florey, 1943; M. E. Florey and Williams, 1944). (No observations have yet been reported on the appearances of bones associated with penicillin-treated war wounds.)

Causes of Failure.—There should be no failure if penicillin is so applied as to be continuously in contact with all infecting organisms in a bacteriostatic concentration, provided also that leucocytes and tissue fluids have access. Under these conditions growth is bound to cease and the infection to be overcome. Apparent failure of the drug to do its work should suggest one of the following defects :—

1. Dead tissue such as a slough or sequestrum is present and is forming a focus of infection. Such tissue should have been removed at the beginning of treatment or in any case as early as possible.

2. An infected area is not being reached by the drug. In systemic treatment a large or thick-walled abscess, or an infected serous cavity will form such an area; good surgical access and local injection of the drug will be called for. In a local infection there may be unsuspected sinuses or other extensions of infected tissue, and these are an indication for further surgical intervention to enable the drug to reach every infected piece of tissue.

3. The dose is too small or application too infrequent.

4. The principal bacteria causing the infection are not sensitive to penicillin.

5. The preparation of penicillin has lost potency and no longer contains the stated number of units. Whether this is so can only be ascertained by a fresh assay carried out by someone experienced in assay work.

In mixed infections much benefit may be obtained by eliminating the sensitive bacteria (usually streptococci or staphylococci) even if insensitive bacteria such as *Ps. pyocyanea* remain. Pus due to insensitive Gram-negative bacilli may persist for a few days, but experience shows that it delays healing very little and that skin-grafts usually take in spite of its presence (Lyons, 1943; Bodenham, 1943; Jeffrey, 1944, a).

Note: This paper surveys only the basic data about penicillin and the references mentioned are not exhaustive. Others will be found in the bibliography at the end of this number.

BACTERIOLOGICAL METHODS IN CONNEXION WITH PENICILLIN TREATMENT

By L. P. GARROD and N. G. HEATLEY

The treatment of patients with penicillin can be conducted satisfactorily only if the services of a bacteriological laboratory are available. The following is an account of the routine investigations which need to be carried out there if treatment is to be directed intelligently. It contains little or nothing new to those who have made a special study of the use of penicillin, but may serve as a guide to those new to this field.

BACTERIOLOGICAL DIAGNOSIS AND SENSITIVITY TEST

Only certain species of bacteria are so sensitive to penicillin that the infections they cause can be successfully treated with it; others are much more or even totally resistant. It is therefore necessary to know in each case what the infecting organisms are before deciding on treatment. It is not, however, enough for this purpose to make a species diagnosis: it is also strongly advisable to determine the sensitivity of the individual strain to penicillin. This varies somewhat within each species, particularly so in *Staphylococcus aureus*, *Streptococcus viridans*, and *Actinomyces hominis*. There are two sorts of method for doing this, one of which combines a sensitivity test with the primary culture, while the other employs a pure culture after isolation.

The Agar Cup Method.—With a sterile No. 5 cork borer two discs are cut from a plate of blood-agar (or whatever other culture medium it may be desired to use) and removed with a sterile wire. The bottom of the hole so formed is sealed with a drop of melted agar to prevent creeping of the fluid subsequently added between the medium and the floor of the plate. The inoculum is then placed on the surface of the medium and spread in the ordinary way. Finally, one drop of a penicillin solution of a strength of 10 units per ml. is placed in one of the holes or 'cups' and a drop of solution of a strength of 1 unit per ml. in the other; the plates are then incubated, medium side downwards. The penicillin diffuses into the surrounding medium, its concentration diminishing with distance from the cup, so that the growth of susceptible bacteria is prevented in a zone surrounding the cup the width of which is a rough measure of their degree of sensitivity. Fleming, who devised this modification of his agar cup method (Fleming, 1942, b), finds that the use of solutions of two different strengths gives better distinction between fully and only moderately sensitive organisms than can be got by using only one. In a mixed culture there are often two zones of inhibition, one affecting both organisms, and the other only one. (*Fig.* 73.)

This method can be used with any agar medium, and for anaerobic as well as aerobic culture. It often enables a full report to be made within 24 hours, and is economical in material as well as time. When large numbers of specimens are being examined from patients undergoing local treatment it may be the only method

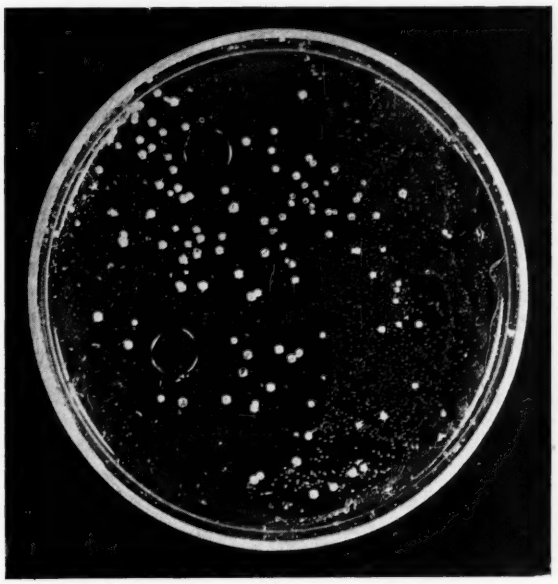

Fig. 73.—Primary culture embodying sensitivity test. The lower cup contains one drop of 10-unit per ml. penicillin solution and the upper cup one of 1-unit per ml. solution. Growth of hæmolytic streptococci (numerous colonies, mainly on the right) is inhibited throughout a wide zone around each cup. The large and much less numerous colonies are of an exceptionally resistant *Staph. aureus*; these grow freely within the area in which the streptococci are inhibited.

for which the laboratory staff has time. A simplification, instead of making and sealing the holes as described, is to spread the plate with the material to be tested, then place two cylinders (as used in the cylinder-plate method below) on the agar and fill them with the respective penicillin solutions.

Somewhat similar methods, having the advantage that the degree of inhibition produced can be compared with that of a standard organism, are the two following:—

a. **The Gutter Plate Method.**—In this method, described by Fleming (1929, 1942, b), a strip of agar is removed from a nutrient agar plate, and the gutter thereby formed filled with molten agar with which has been incorporated some penicillin (the strip removed from the plate can be melted down in a sterile test-tube and penicillin added to give a final concentration

of about 5 units per ml.). When the agar has solidified loopfuls of the patient's organism and, for comparison, of an organism of known sensitivity are streaked across half the plate at right angles to the gutter. The plate should be dried, either before or after streaking the organisms, and incubated at 37° C. for 12–24 hours. There will be good growth at one end of the streaks, but it will terminate at points whose distance from the edge of the gutter will vary inversely with the sensitivity of the organism to penicillin. Six or more different organisms may be tested on the same plate.

b. **The Cylinder Method.**—This has been adopted by several workers independently. An open-ended cylinder or ring such as is used for assay (*see below*) is momentarily warmed and then placed on the surface of a nutrient agar plate. Into the cup thereby formed are placed a few drops of penicillin solution containing 1–100 units per ml., and loopfuls of patients' and standard organisms are streaked radially from the cylinder to the edge of the plate, which is dried, if necessary, and incubated. The penicillin diffuses into the agar, and the relative sensitivity to it of the different organisms is indicated by the distance from the cylinder at which their growth ceases.

The above methods—or modifications of them (e.g., with strips or discs of filter paper soaked in penicillin)—will show whether the sensitivity of the patient's organism is equal to, less then, or greater than that of a standard organism. If a quantitative comparison of sensitivity is required, other methods must be resorted to, such as the following :—

a. A series of broth dilutions are made containing known amounts of penicillin in falling concentrations. The tubes are inoculated with the patient's organism and incubated for 12–24 hours. The most dilute tube in which growth is prevented gives directly the concentration of penicillin which will just inhibit the organism. This value may vary by 100 per cent or more according to the conditions of the test, so it is advantageous to compare the end-point with that in an exactly similar series of tubes inoculated with an organism of approximately known sensitivity.

b. A series of agar plates made up to contain falling concentrations of penicillin are each streaked with patient's organism, and incubated for 12–24 hours. The lowest effective concentration of penicillin is usually taken as that in the plate on which the growth of the organism has been almost completely inhibited. This method has the advantages over the tube dilution method above that (*a*) an absolutely pure culture of the patient's organism is not essential, and (*b*) several different organisms can be examined on the same series of plates at the same time. The plates may be prepared by placing different known amounts of penicillin solution and water to make a total of, say, 2 ml., in each of a number of sterile Petri dishes, then adding, say, 10 ml. of agar and thoroughly mixing before allowing to solidify. The plates are dried off before use. Here again the end-point depends on the conditions of the test, so it is desirable to make streaks of an organism of approximately known sensitivity, as well as of the patients' organisms.

CULTIVATION OF MATERIAL FROM CASES UNDER TREATMENT

It is advisable to make further cultures at intervals during treatment in order to determine whether the infection is being eliminated. The material to be cultivated, especially if derived from a lesion undergoing local treatment, may contain a good deal of penicillin which could in some circumstances prevent the growth of bacteria still surviving in it. If the material is pus, of which only a small loopful is sown on a plate, the amount of penicillin likely to be present will rarely do more than prevent growth over a small area where the inoculum is thickest. If it should be necessary to cultivate larger volumes of such material, or of cerebrospinal fluid or urine containing penicillin, or in making blood-cultures from patients undergoing systemic treatment, the penicillin in the inoculum can be destroyed by adding a sterile preparation of penicillinase. This is an enzyme formed by certain penicillin-resistant bacteria (Abraham and Chain, 1940), and methods for preparing and using it for this purpose have been described by Harper (1943) and Duthie (1944). Duthie's preparation, which is easily made and is stable and convenient for routine use, contains the enzyme *in solution* and can therefore be sterilized by Seitz filtration.

If a combination of penicillin and a sulphonamide has been used in treatment, material to be cultivated may also contain the latter. The possible inhibitory action of the sulphonamides may be neutralized by adding *p*-aminobenzoic acid to the culture medium in a concentration of about 5 mg. per 100 c.c. (Janeway, 1941.)

STANDARDIZATION OF POTENCY; THE OXFORD UNIT

Penicillin at present available for clinical purposes contains a good deal of inactive impurity (usually of unknown composition, but essentially non-toxic). As the proportion of penicillin to impurity varies widely, estimation of dosage, etc., on a purely weight basis is useless. The amount must be specified in terms of the antibacterial power of the preparation, and this is usually expressed in terms of the 'Oxford unit'—a purely arbitrary unit defined originally (Abraham et al., 1941) as *the amount of penicillin which when dissolved in 1 ml. of water gives the same inhibition as . . .* [a certain partially purified] *standard* [solution]. Dry preparations in England, America, and elsewhere have been standardized against this original solution, either directly or indirectly.

Contrary to statements of certain workers, Abraham et al. (1941) did not define a unit as the amount of penicillin which in 1 ml. of water gave a zone of inhibition 24 mm. in diameter by the cylinder-plate method. Some confusion may have been caused, however, by the statement by Florey and Jennings (1942) that " for those using the dilution method it may be stated that the ' Oxford unit ' is that amount of penicillin which when dissolved in 50 ml. of meat extract broth just inhibits completely the growth of the test strain of *Staphylococcus aureus* ". This method of standardization, though it may give consistent results in the hands of any one group of workers —but see Foster and Woodruff (1943, a)—is subject to many variables, and cannot be taken as necessarily accurate under the conditions prevailing elsewhere.

METHODS OF ASSAY OF PENICILLIN

For clinical purposes it will usually be sufficient to proceed on the assumption that any commercial preparation contains the stated number of units. Occasions may arise, however, when this must be checked, e.g., in the case of material being used some time after the expiry date, or if it has been subjected to adverse storage conditions; or perhaps if poor clinical response cannot be explained in any way other than by the possibility of deterioration of the product.

Several different methods of estimating potency have been used, including the following:

1. Titration in broth, compared with a solution of known strength, taking as the end-point: (*a*) Complete prevention of growth (Fleming, 1929, 1942, b; Hobby, Meyer, and Chaffee, 1942, a; Foster and Woodruff, 1943, a; Schmidt and Moyer, 1944; McKee, Rake, and Menzel, 1944); (*b*) Diminution of growth to a known extent—usually to 50 per cent opacity of the control; (*c*) Suppression of suspended, as opposed to sedimentary, growth; (*d*) Prevention of hæmolysin formation (Rammelkamp, 1942; Rake and Jones, 1943; Wilson, 1943); (*e*) Change in *p*H of the medium (Fleming, 1942, b).

2. Titration on agar plates containing falling concentrations of penicillin (Foster and Woodruff, 1943, a).

3. Turbidimetric methods (Pope, unpublished; Foster, 1942; Foster and Wilker, 1943; Joslyn, 1944; Lee, Foley, Epstein, and Wallace, 1944).

4. The cylinder-plate method (Abraham et al., 1941; Foster and Woodruff, 1943, a, b, 1944; Epstein, Foley, Perrine, and Lee, 1944; Heatley, 1944; Schmidt and Moyer, 1944).

It is not possible in a brief review to give full working instructions for each of these methods, for details of which the original papers must be consulted. The method of choice will depend on circumstances, but unless only a semi-quantitative estimate of potency is required, it is highly desirable that a standard penicillin solution containing a known amount of penicillin should be set up at the same time as the unknown, so that the potency of the latter may be expressed in terms of the standard. If a certified standard preparation is not available it is suggested that the use of any product from a reputable source containing a stated number of units is preferable to an assay conducted without any standard. Providing the principle of comparing with a standard is adhered to, any assay method is, *within its own limits*, equally good, but the following are recommended.

Broth Dilution Method.—Where an estimation of potency is only rarely required, the tube dilution method is probably the easiest, the technique being one with which the bacteriologist is already familiar. Serial dilutions in a suitable broth of the unknown and of a standard preparation are made, and the tubes are inoculated with a test organism such as *Staph. aureus* or *Str. pyogenes*. then incubated at 37° C. for 12–48 hours. The end-point is usually taken as being between that tube which just prevents growth completely (or which prevents suspended as opposed to sedimentary growth) and the first in which some growth occurs, but whatever the end-point the potency of the unknown can be expressed in terms of the standard. Many workers have assumed that if the test is carried out with the same organism under the same conditions, the end-point will always correspond to the same concentration of penicillin. This may be true in certain cases, but emphatically it cannot be relied on because: (*a*) it is difficult and tedious to reproduce conditions exactly and considerable variation may occur in the end-points obtained in different laboratories where the conditions are apparently identical; and (*b*) evidence is accumulating to show that in the same laboratory under identical conditions a given strain of test organism may show a drifting or a sudden variation in susceptibility to penicillin which will vitiate quantitative work.

Fleming (1942, b) has suggested that peptone-water containing glucose be used (as it is more easily reproducible in different laboratories than broth), and that the end-point be taken as a change or absence of change in *p*H, as shown by Andrade's indicator.

The end-point in a broth dilution series may also be assessed by using a hæmolytic streptococcus as test organism, red cells being used to indicate hæmolysis.

Unless special precautions are taken the degree of accuracy obtainable with dilution tests usually is not high, either because the steps in the dilution series are large, or, if the interval is reduced, the end-point may not be sufficiently sharp to distinguish with certainty which of two (or more) tubes mark it. A sharper end-point can be obtained if instead of ordinary broth a papain digest of horse muscle containing 0·2 per cent glucose is used (Pope, unpublished).

Turbidimetric Methods.—This type of method would seem capable of high precision,

and might under certain circumstances be the method of choice provided a suitable photometric apparatus were available. Usually a curve relating the light transmitted to the penicillin concentration is constructed from the readings obtained from solutions containing known amounts of penicillin. The concentration of penicillin in the unknowns is then read off from this curve. Foster and Wilker (1943) report in some detail the effect of varying the conditions when *Staph. aureus* is the test organism.

Dr. C. G. Pope (unpublished method), using the papain digest medium mentioned above, obtains with *Staph. aureus* a considerably steeper turbidity-penicillin concentration curve than with most other media. The curve, sigmoid in shape, has an unusually long and straight central portion and by extrapolating this back to the axis representing penicillin concentration a very high degree of accuracy is obtainable.

Cylinder-plate Method.—Where assays have to be made more often—either of fresh penicillin or of body fluids such as urine containing not less than about 0·2 units per ml.—the cylinder-plate method is worth adopting, This was first described by Abraham et al. (1941); later, in more detail, by Heatley (1944). Variations of it are described in considerable detail by Foster and Woodruff (1944) and by Schmidt and Moyer (1944), both of which groups recommend it as the most practical method for routine use. The method is largely empirical and it is impossible to give in detail all the minor modifications in use—much less to assess their effect on the accuracy of the method. In the following account the aim has been to describe the broad outlines whilst at the same time giving sufficient details to enable the test to be carried out satisfactorily, and to indicate the limits within which some of the conditions may be varied.

Principle.—An agar plate is uniformly seeded with the test organism. Short open-ended cylinders of glass or vitreous porcelain are placed on the surface of the agar and filled with the solution to be tested (or with a standard). The plate is then incubated and will exhibit a uniform bacterial growth except for a circular zone around each cylinder where the penicillin has diffused out and prevented growth. The diameter of this zone of inhibition is related to the concentration of penicillin, the exact relation being found by setting up with the unknown an appropriate range of solutions containing known amounts of pencillin.

Composition of Agar.—Any simple nutrient agar may be used, but—at any rate where *Staph. aureus* is the test organism—the addition of phosphate buffer *p*H 6·5–7·0 in a final concentration of 0·02–0·1 molar, gives sharper zones of inhibition and more uniform results.

Test Organism.—Any sensitive strain of *Staph. aureus* may be used. In actual practice a strain known as *Staph. aureus* H (the Oxford H staphylococcus), now No. 6571 of the National Collection of Type Cultures, is largely used in England and in some laboratories in America; in the latter country the Food and Drugs Administration *Staph. aureus* No. 209 (No. 6718 of the National Collection of Type Cultures) is also extensively used. Foster and Woodruff (1944), in a method for which several advantages are claimed, use an unspecified strain of *B. subtilis*, and Dr. C. G. Pope (unpublished) uses a quick-growing organism of the *B. subtilis* type which enables results to be read within 3 hours of setting up.

Method of Seeding Plates.—The inhibitory power of penicillin, unlike that of the sulphonamides, is not greatly affected by the number of organisms present, so the density of seeding is not an important factor. Slightly larger zones are, however, formed when the density of seeding is low. Two methods of seeding are in use:—

a. Molten agar is preseeded with a small amount of a broth culture of *Staph. aureus* just before pouring the plates, or with a spore suspension of *B. subtilis*. The latter organism has the distinct advantage that careful cooling of the agar before seeding is not necessary. Schmidt and Moyer (1944) pour the plates in two stages, first with 20 ml. of sterile agar, then when this has solidified, with 3 ml. of agar seeded with *Staph. aureus*.

b. A broth culture—or a 1–10 to 1–1000 dilution of a broth culture—of the test organism is flooded on to an ordinary plate and thoroughly spread by tilting and rocking. The excess fluid is drained to one side (which is marked, for reasons given below) and is removed. The plate is then dried by placing in the 37° C. incubator for 1–2 hours on a special drying stand (*Fig.* 74) which enables the lid to be supported 1·0–1·5 cm. above the bottom of the dish. If not to be used for an hour or so the plates are placed in the refrigerator, where they may be stored unimpared for some days.

FIG. 74.—Stand for drying plates.

Drying of the plates is not mentioned by Foster and Woodruff, but Schmidt and Moyer (1944) specify that the glass lids of the Petri dishes be replaced by porous covers for 45–60 minutes immediately after the plates have been poured. Where *B. subtilis* is used it is important that the plates are used as soon as they have been poured or else placed in the refrigerator till required.

Cylinders.—Provided they are uniform, the actual dimensions of the cylinders are not important—8–10 mm. tall by about 7 mm. external diameter is a convenient size.* The lower ends

* Suitable vitreous porcelain cylinders can be obtained from James Macintyre & Co. Ltd., Waterloo Road, Burslem, Staffs., England. Their lower edge should be ground level before use.

need not be bevelled as originally specified, but they must be ground perfectly level and smooth, so that fluid-tight seals are obtained when they are placed on the agar. Such a seal may be assured by momentarily flaming the cylinder just before placing on the agar, but if overheated it will sink into the agar and give a falsely small zone of inhibition. Usually eight cylinders are arranged peripherally on a 4-in. plate, and it is better to avoid the centre of the plate where the agar is often thinner than elsewhere.

Making up Solutions for Test.—The solutions to be tested need not be sterile, and the presence of ether, chloroform, or amyl acetate has no appreciable effect on the results. It is recommended that phosphate buffer *p*H 6·5–7·0 and 0·02–0·1 molar be used for making up the solutions, which should have between 0·3 and 2·0 units per ml. of penicillin. With less sensitive organisms, e.g., with Dr. Pope's quick-growing *B. subtilis* type, the range covered will be higher.

Filling the Cylinders.—The amount of fluid in the cylinders has little effect on the results obtained, but in practice they are filled level with the top, care being taken to prevent the formation of an air space between the agar and the fluid. A Pasteur pipette is useful for filling the cylinders.

Arranging the Samples on the Plates.—Samples should be set up at least in duplicate. Where the plates have been seeded by the flooding method the position of the samples is important because occasionally the zone size with any given solution of penicillin may be appreciably smaller (or larger) at that side of the plate to which the seeding fluid was drained, than at the opposite side. The reasons for this are varied and complicated. Errors from this effect—which occurs seldom—can be minimized or eliminated by arranging the samples so that the replicates of each are symmetrically disposed with regard to the side to which the fluid was drained. For example, if the samples are to be set up in triplicate, they are kept in the same order but are begun 120° farther round on each successive plate, with respect to the side to which the plate was drained; if in quadruplicate, the samples should start 90° farther round on each successive plate. When the plates are bulk-seeded this occasional asymmetrical response presumably does not occur.

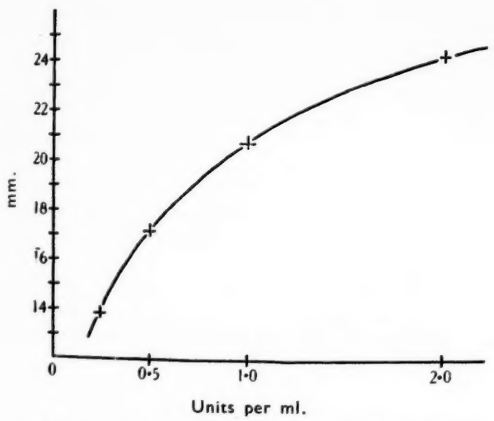

FIG. 75.—Typical curve relating diameter of zone of inhibition with concentration of penicillin solution causing it.

Establishment of Standard Curve.—Solutions in buffer of a standard penicillin are made up containing 2·0, 1·0, 0·5 (and sometimes 0·25) units per ml. These solutions are placed one set on each of four of the assay plates (assuming that the assay is being carried out in quadruplicate), and the unknown solutions are filled into the remaining cylinders of these and other plates. After incubation and measurement of the zone sizes (*see below*), a curve can be constructed showing the relation of zone diameter to number of units per ml. in the solution in the cylinder (*Fig.* 75). From this curve the number of units per ml. corresponding to any zone size (within the range used) can be read off and the potency of the original solutions or powders calculated.

For the highest accuracy it is recommended that a fresh curve be made for each batch of assays which should, of course, be made on plates all poured at the same time.

Incubation of Plates.—The plates are incubated at 37° C. in the case of *Staph. aureus*, and at 30° C.

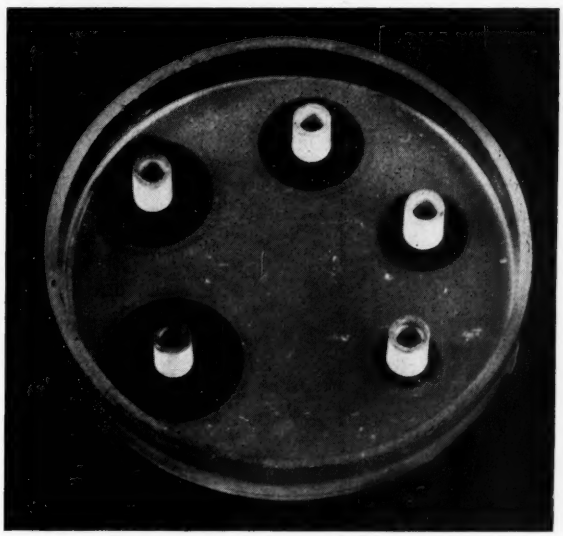

FIG. 76.—An assay plate surface-seeded with *Staph. aureus*. The cylinders contained 4, 2, 1, 0·5, and 0·25 units of penicillin per ml.

or less where *B. subtilis* is used. If the plates are placed on a piece of wood or asbestos sheet, and thus transferred to the incubator, there is no danger that water may condense on the lid of the dish and drop back on to the agar. The plates are usually incubated overnight, but zones of inhibition can be read after less than 10 hours (or with a quick-growing organism incubated at 37° C., after 4–5 hours). With *Staph. aureus* the zones increase very slightly in size when incubation is prolonged, but as the standard and

unknown zones are read at the same time this does not affect the assay. Somewhat larger zones of inhibition are formed with *Staph. aureus* if the plates are kept in the ice chest for some hours before incubation, a report of which effect is given by Schmidt and Moyer (1944). (*Fig.* 76.)

Measurement of Zones of Inhibition.—This may be done by turning the plates over and measuring the zone directly with a millimetre scale, or the plate may be observed on a black background carrying a well-illuminated scale; or the diameter may be taken with dividers or screw callipers and measured against a paper or other scale.

Accuracy.—This was investigated with *Staph. aureus* as test organism by Heatley (1944), who quotes three series of consecutive assays of (three) unknown solutions against a standard. These series, containing 27, 10, and 10 observations, each derived from a quadruplicate assay, had coefficients of variation of 9·0, 5·0, and 5·6 per cent respectively. This means that in the first series (which shows the biggest scatter) only once in twenty times is a quadruplicate assay likely to differ from the true value by more than ± 17·6 per cent. For assays in duplicate or triplicate (i.e., from the measurement of two or three zones), the limits will be ± 24·9 and 20·3 per cent respectively. (The figures of ± 19·6, 27·7, and 22·7 per cent quoted in this connexion by Heatley (1944) are incorrect.)

Schmidt and Moyer (1944), also using *Staph. aureus*, believe that "the method may be in error 15 to 20 per cent". Foster and Woodruff (1944), using their *B. subtilis* method, consider that the precision "can be taken as nearer ± 15 per cent". The latter authors give a series of 15 assays made on one sample over a period of 14 months which shows a scatter somewhat greater than the first series mentioned above, but insufficient details are given to show whether this comparison is justified.

Substitutes for Cylinders.—The use of circles of filter paper or filter fabric instead of cylinders has been suggested by Dowdy, Vincent, and Vincent (quoted by Foster and Woodruff, 1943, a), Pope (quoted by Heatley, 1944), and Epstein, Foley, Perrine, and Lee (1944). The latter authors also recommend the use of a few large Pyrex baking dishes in place of large numbers of Petri dishes.*

Rapid Methods of Assay.—Methods of assay by which the result can be obtained within an hour or a few hours instead of after overnight incubation can be of great value in the manufacture of the drug, but are unlikely to have any application in clinical work. For the sake of completeness, however, the following references to rapid methods of assay are given:—

Dilution methods: Using as end-point the suppression of hæmolysin formation by hæmolytic streptococci—Wilson, 1943 (3–4 hours); Rake and Jones, 1943 (60–90 minutes).

Turbidimetric methods: Foster and Wilker, 1943 (with *B. adhærens*, 4–5 hours); Joslyn, 1944 (4 hours); Lee, Foley, Epstein, and Wallace, 1944 (90 minutes).

Cylinder-plate method: Pope, unpublished (3 hours).

ASSAY OF PHARMACEUTICAL PREPARATIONS

Apart from simple aqueous solutions, penicillin may be dispensed in dusting powders, snuffs, ointments, and creams. The ointments and creams have often been reported as being much less stable than the plain aqueous solution, so an assay of penicillin in such samples may sometimes be required. The presence of other medicaments might conceivably cause difficulties, otherwise the following procedures may be used.

a. **Dusting Powders, Snuffs, etc.**—These can usually be treated as dry penicillin. If sulphonamides are present care must be taken to see that *p*-aminobenzoic acid is included in the media used.

b. **Ointments, Creams, etc.**—A very rough indication of the amount of penicillin present in preparations of this sort is given by the width of the zone of inhibition around a blob of the material incubated on the surface of a plate seeded with a sensitive organism (Ruehle and Brewer, 1931). A similar but preferable method is to fill a cup in an agar plate with the material (the cup being made in the same way as for a sensitivity test, q.v.) taking care that it is in contact with the wall of the cup all round.

A more accurate result is obtained by shaking a known amount of material with a known volume of dilute phosphate buffer and—particularly if the cream is of the water-in-oil type—some solvent to disperse the non-aqueous phase. The buffer extract, separated if necessary by centrifuging, is diluted and assayed by any convenient method.

ASSAY OF PENICILLIN IN EXUDATES AND OTHER BODY FLUIDS

Pus, urine, and cerebrospinal fluid from cases under treatment may contain a fairly high concentration of penicillin, such that its presence can readily be detected and an approximate estimate of its quantity be obtained by one of the agar diffusion methods. The cylinder-plate or agar-cup methods are therefore applicable, but their results should not be accepted on too exact a quantitative basis: possible disturbing factors are the effects of viscosity in pus and of the presence of other bacteria, which produce either penicillinase or an antibacterial substance of their own (e.g., *Ps. pyocyanea*, Medical Research Council, 1944). A more satisfactory method, not yet completely worked out, would be to extract the material with amyl acetate after dilution if

*Since going to press, the following papers dealing with the filter paper disc technique have been received: Sherwood, Falco, and De Beer, 1944; Vincent and Vincent, 1944.

necessary and acidification to *p*H 2·0–2·5, to separate the amyl acetate by centrifugation, extract this with buffer solution, and assay the penicillin in this by any of the usual methods.

Urine from patients receiving systemic treatment contains a large amount of penicillin, which can be titrated by any of the methods used for the assay of penicillin itself. If the specimen has to be stored, Seitz filtration (Rammelkamp, 1942) or extraction into a solvent as above, is advisable, although it will *usually* retain its activity if shaken with chloroform and refrigerated. If not filtered or extracted it should be assayed as soon as possible after collection.

THE ASSAY OF PENICILLIN IN BLOOD

The clinician often requires to know whether or not the blood of a patient receiving penicillin contains sufficient to prevent the growth of the infecting organism. This type of assay presents special difficulties, for the concentration of penicillin in the serum may be so low that any appreciable dilution, e.g., with broth, will reduce it below the level at which it can be detected. Methods have, however, been published by Rammelkamp (1942) and Fleming (1943) which have been used for the semi-quantitative estimation of penicillin down to concentrations as low as 0·02 units per ml.

In Rammelkamp's method, which has been used for the assay of penicillin in whole blood, erythrocytes, urine, exudates from empyema cavities, joint fluid, etc., the test organism is a particularly sensitive hæmolytic streptococcus. Serial dilutions (usually twofold) are made in veal infusion broth in small tubes, the final volume in each being 0·2 ml. To the tubes are then added 0·5 ml. of veal infusion broth containing 1000–10,000 organisms per ml. and 1 per cent of erythrocytes. The tubes are incubated for 18 hours, then examined for hæmolysis, the absence of which usually means that the culture is sterile. The end-point is compared with that in a similar series of tubes containing known amounts of penicillin.

In Fleming's method serial dilutions of the patient's serum, cerebrospinal fluid, or other fluid are made in small tubes or on a sterile waxed slide, a micropipette of 25–100 c.mm. capacity being used. To each dilution are then added —from a waxed pipette—2·5 c.mm. of a suitable dilution of the test organism (staphylococcus or streptococcus) and the mixtures are run into slide cells (Colebrook, Storer, and Wright, 1923; Bigger, Thomas, and Caldwell, 1944) which are sealed and incubated. When staphylococci are grown in serum, or in serum diluted in normal saline up to 1–100 or more, the developing colonies are not diffuse, but in compact masses which can be readily recognized with a hand lens or even with the naked eye. For best results the test organism culture should be so diluted that there are 15–50 viable organisms in each compartment of the slide cell. Alternatively the dilutions may be incubated in sealed capillary tubes instead of in slide cells. Another variation used by Fleming (1943) is to prepare serial dilutions of the patient's serum as before, then to mix an equal volume of normal human blood infected with *Str. pyogenes* with each dilution, run into slide cells, seal, and incubate. No hæmolysis occurs in those cells where the growth of the organisms is prevented. (It is important that the natural bactericidal power of the blood be abolished by (*a*) removing the leucocytes, (*b*) heating to 50° C., (*c*) adding liquoid to a concentration of 1–1000, or (*d*) keeping the blood for more than 2 days.) (*Fig.* 77.)

For nearly two years we have used a slight variation of the above method which has given satisfactory results. A drop of the patient's blood, obtained by sterile needle-prick, is collected in a sterile capillary tube which is sealed, allowed to clot, and centrifuged. A drop (5–10 c.mm.) of patient's serum is placed directly on one end of a sterile slide which already bears three or four drops of the same volume of normal serum. With a second drop of the patient's serum, these normal drops are made into a twofold dilution series, the last drop of normal serum being untouched and left as control. One of us (N. G. H.) has measured these drops with a pipette of the type described by Milton Levy (1936); a simpler and sufficiently accurate method is to take the drop as delivered by a Pasteur pipette as the unit of volume. The drops are inoculated with a small loopful (about 0·5 c.mm.) of a 1–1000 dilution of a 16–24 hour broth culture of *Staph. aureus*. Each drop is then covered with a sterile coverglass, which is sealed at the edges with molten vaseline, and the slide is incubated for 24 hours. A similar series may be set up with known amounts of penicillin, but for clinical purposes this is not usually needed. In those drops containing more than an inhibitory

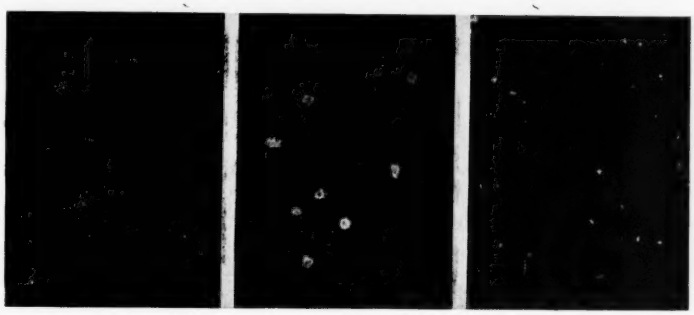

FIG. 77.—Slide assay of penicillin in blood. Appearance of staphylococcal colonies (× 7) after 24-hours' incubation in serum. A, Control; B, Partial inhibition—fewer and larger colonies; C, Complete inhibition.

concentration of penicillin, no colonies will develop; where the concentration of penicillin is nearly inhibitory, the number of colonies will be markedly less than in the control drop, and where the concentration is of the order of half or less of the minimum required for complete inhibition, there will be approximately as many colonies as in the control.

By combining Fleming's type of dilution technique and a sensitive test organism such as the hæmolytic streptococcus used by Rammelkamp, it should be a simple matter to increase the sensitivity of the test three or four fold (i.e., to a lower limit of 0·005 units per ml.).

The photographs were taken by Mr. H. Axtell.

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APPLICATION OF PENICILLIN TO WAR WOUNDS

BY J. S. JEFFREY, LIEUT.-COLONEL, R.A.M.C.

No active war surgeon doubts that the treatment of battle casualties demands the intelligent combination of resuscitation, operative surgery, and chemotherapy. I am not concerned here with the first two aspects, except to say that, while careful operative surgery is of paramount importance, no amount of wound excision can by itself get rid of infection in the vast majority of cases. It is possible that if one is prepared to sacrifice much viable tissue by a wide block dissection some wounds may be rendered sterile, but such a procedure is unjustifiable in routine war surgery.

Sulphonamide chemotherapy has been of great value in the fight to control infection in this war: and we are now faced with the problem of how to make best use of penicillin, and, equally important, how to prevent misuse. With its specific action against the common organismal invaders of war wounds (staphylococci and clostridia in the early stages, and streptococci in the later stages) penicillin is the most effective and least harmful agent yet discovered, both as a systemically-administered drug and as a local antiseptic, and there is everything to be gained by making use of the proper combination of surgery and penicillin.

The object of using penicillin routinely in battle casualties is to save lives; and to minimize functional disability and loss of man-power. By controlling infection it allows a more rapid healing of the wound than has generally been possible in war wounds hitherto. If the wound can be sutured at an early stage scar tissue is reduced to a minimum: this increases the range of function in an otherwise normal part, and makes easier the subsequent repair of nerve and other injuries if they have not been repaired at the time.

GENERAL INDICATIONS FOR THE USE OF PENICILLIN

Penicillin has three main spheres in war surgery: (1) To *prevent* infection of the wound soon after wounding (i.e., at the medical units in the Forward Areas); (2) To *control* infection in the first two weeks (i.e., at the Forward Base Hospitals); and (3) To *combat* sepsis in the later stages.

1. Prevention of Infection.—In the British Army in Italy it was the practice at the first operation at the Casualty Clearing Station level to insufflate penicillin-sulphathiazole powder (5000 units per gramme) throughout the wound on completion of the wound excision. The wound was left open, insufflated with powder to form a thick hoar-frost (average 2–4 g., i.e., 10,000—20,000 units penicillin), covered with vaseline gauze, and immobilized for the journey. Primary suture of wounds in the Forward Areas, where the patient cannot be retained, is always dangerous and was never permitted.

On the question whether this wound insufflawas effective, there is this evidence (Fraser et al., 1943): 100 wounds were so treated at Casualty Clearing Stations in Sicily (average operation time after wounding, 10 hours) and not disturbed until they reached a Forward Base Hospital in Tripoli five days later. Exactly 50 per cent showed no growth on culture when unveiled at Tripoli. A comparable series of 100 wounds were insufflated with sulphanilamide powder and 17 per cent showed no growth on arrival at Tripoli. This is an experiment that ought to be repeated, because the dressings in a few of the contrast series were disturbed in transit. A group of penicillin-treated cases that did not arrive until eight days after insufflation were infected with Gram-positive organisms, which indicated that the single preliminary insufflation was insufficient to control infection over that longer period.

In Italy there was widespread favourable clinical impression that the penicillin-treated wounds were clean on arrival at the Forward Base; but it is desirable that this point should be verified by further clinical experiment, for considerable quantities of calcium penicillin can be expended in this manner.

2. Control of Infection.—At the Forward Base Hospitals the decision should be taken as

to what type of case requires routine penicillin therapy, and whether treatment is to be by systemic administration or local application (*see below*). It is at this level of evacuation that greatest value can be expected from penicillin. The tissues are fresh, the infection is recent, the organisms are not shut away in fibrous tissue and sequestra and have not become intractable and insensitive to chemotherapy. Furthermore, unless there is great pressure on bed space, the patient can be retained long enough for the bacteriostatic action of the drug to be effective.

3. Combat of Sepsis.—In the case with established sepsis several weeks or months after wounding, penicillin by itself is disappointing. Properly allied to other procedures it can be of value, i.e., in combination with surgical drainage of abscesses and removal of dead matter, blood transfusion, control of avitaminosis and hypoprotinæmia, and other general measures. There is need at this level always to test the organism present for sensitivity to penicillin, for about 5 per cent of staphylococci are resistant.

INDICATIONS FOR SYSTEMIC THERAPY

In general, systemic therapy is the method of choice in large traumatized areas that are inaccessible to local powder or solution and accessible only to the drug circulating in the blood-stream. This involves most of the severe casualties : fractures, gas gangrene, septicæmic states, amputation stumps, multiple severe flesh wounds, etc. (*see Fig.* 78). Penicillin is usually not of value in penetrating wounds of the abdomen ; most of the deaths in such cases are due to physiological causes. Straightforward soft tissue conditions require a minimum of three days' continuous treatment ; where there is bone involvement, or infection is shut away in fibrous pockets, the course must extend to five days or longer. These are bare

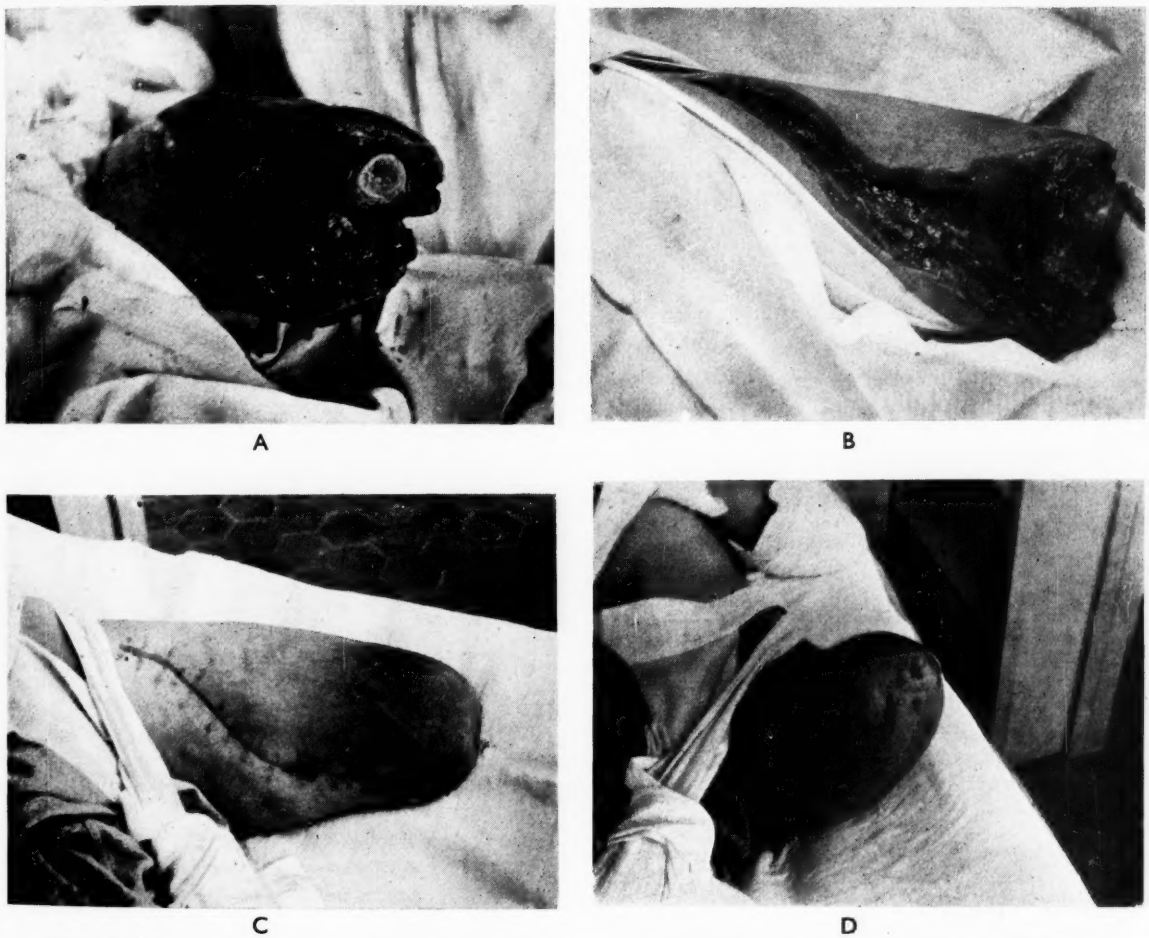

FIG. 78.—*Capt. R.* Closure of an infected amputation stump, with systemic penicillin. A mid-thigh amputation had been performed for gas gangrene of leg. During dressing of the stump five days later the remaining sartorius muscle was found gangrenous. A, Stump at time of dressing and excision of sartorius, before beginning course ; B, After 5 days' systemic penicillin, 540,000 units, and prior to amputation of a further 1 in. of femur and complete wound suture ; C, D, Four weeks after suture.

minimum figures, and it is valueless to use less, and one must be prepared to use more. Infection can easily flare up again if the treatment is cut short. With these figures and facts as a guide, the individual case must be judged on its merits as to the length of the course. The general condition of the patient is of help in this decision, including the temperature chart, which may be unreliable, however, if the drug is being administered intravenously. The state of the wound and a culture from it at the proposed end of treatment can be of great value, although on general principles it is

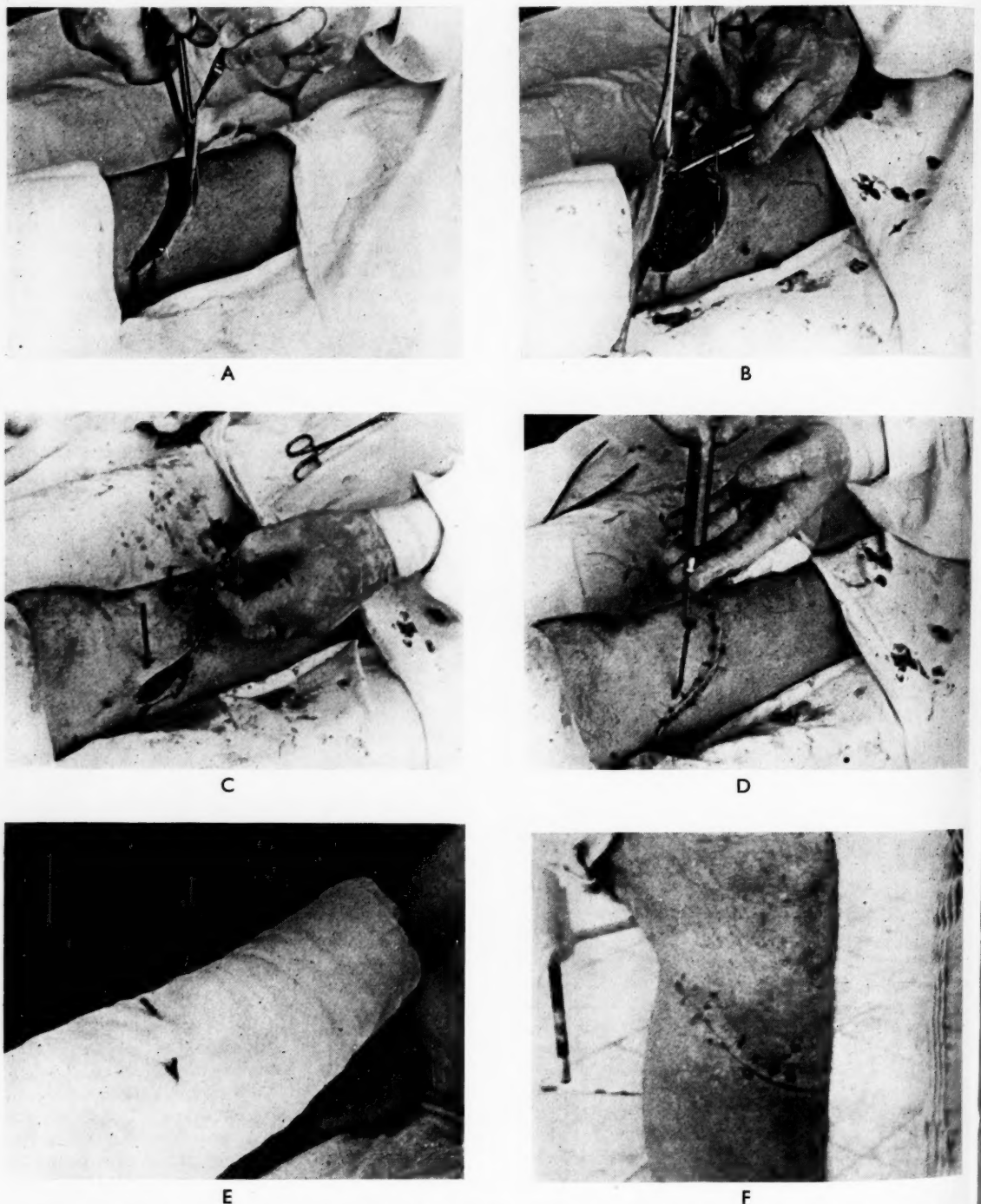

FIG. 79.—*Pte. B.* Illustrating wound excision and suture with tubes at a Forward Base Hospital, four days after wounding. A, Excision of skin edges; B, Undercutting to allow approximation; C, Two tubes into this medium-sized wound, stitched to stab holes; D, Instillation at the end of operation, 5 c.c. down each tube (250 units per c.c.); E, Tube ends uncovered twice daily for instillations, 3 c.c. each tube; F, 28 days after wounding.

inadvisable to make repeated inspections of the wound.

Provided penicillin is in ample supply and there is an efficient staff to cope with the administration, it might be thought advisable policy to prolong the course of treatment indefinitely in order to be on the safe side. Two factors weigh against such a policy: discomfort to the patient through constant injections (though continuous intramuscular and intravenous therapy can minimize this); and the danger that the surgeon may succumb to the feeling that so long as the patient is getting his penicillin all is being done that needs to be done.

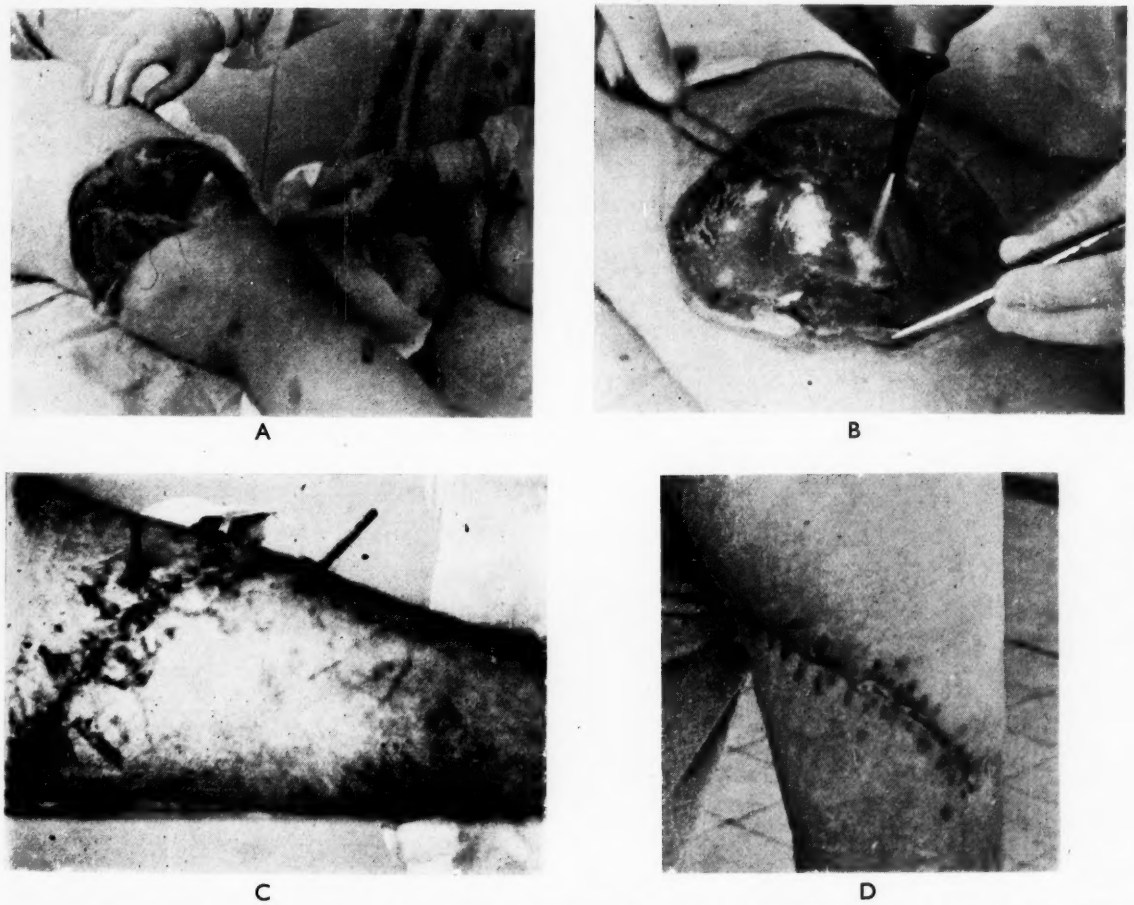

FIG. 80.—*Pte. M.* Shell wound of thigh, which had been widely opened and hamstring muscles divided at a Casualty Clearing Station for suspected gas gangrene. The infected wound was cleaned by daily insufflations of penicillin-sulphanilamide powder (2000 units per gramme) for two days, followed by suture with tubes and instillations on third day. It might have been sutured over a third insufflation, but tubes were thought safer because of the many crevices in the wound. A, Wound after two-days' insufflation and immediately prior to suture (12 days after wounding); B, Insufflating to form a thick hoar-frost; C, Prior to removal of tubes, 5 days after operation—wound stained with Gram-negative pus and blood; D, Patient walking, 34 days after operation, 46 days after wounding.

INDICATIONS FOR LOCAL THERAPY

There are two broad series of cases in which local treatment is the method of choice: (*a*) in cases where systemic treatment is ineffective; and (*b*) where systemic treatment is undesirable.

a. There are certain lesions to which the drug cannot gain access when it is circulating in the blood-stream (i.e., when given systemically). This applies to some of the body membranes through which penicillin either cannot pass or does so in too small a concentration to be effective. Affections of the brain, spinal cord, and meninges; intrapleural lesions; and joint lesions should be treated for choice by local application of penicillin in solution or powder form, and combined with systemic treatment when there is a concomitant septicæmic state or where there are associated injuries outside the membranes.

There is an indication, too, for local instillation of penicillin into abscess cavities, and into large dead spaces such as may occur in a fracture with much bone loss.

b. In soft-tissue wounds and minor fractures local application is as effective as systemic treatment; and is decidedly more comfortable for the patient and more economical.

In Italy the widespread use of locally-applied penicillin made it possible to perform early secondary suture on any mechanically suitable soft-tissue wound. Thus, in 500 wounds specially investigated suture was successful in over 90 per cent, and the failures were only relative in that no man was worse off. (Contrast series using sulphanilamide gave 60–70 per cent success.) This is one of the most useful applications of penicillin in war surgery, for it enables combatant soldiers to return to duty at the earliest possible time. It was estimated that the average time for return to duty of a man with a medium-sized soft-tissue wound was six weeks after wounding if successfully sutured, and twelve weeks if the wound was allowed to heal by granulation or was repaired at a later date. This saving of man power is considerable when it is appreciated that these soft-tissue wounds of limbs and trunk constitute nearly half of all war wounds.

ORGANIZATION

Because the drug is at present far from being simple and foolproof to handle, it is most desirable that every hospital using penicillin should detail a special team to be responsible for administering it. This is essential if many patients are under treatment simultaneously. In British hospitals in Italy the Transfusion Officer and his assistants were made responsible for the dispensing of the drug and its actual administration. Daily they made up the requisite amount of penicillin for the cases under treatment. For example, for each patient on a systemic course of penicillin at the dosage in common vogue, 90,000 units were dissolved in 18 c.c. distilled water in a sterilized glass screw-capped bottle. This was sufficient for six 3-hourly intramuscular injections of 15,000 units each, from 9 a.m. to midnight, and these injections were given by the Transfusion Orderlies. For night work the individual doses were put up in suitable bottles and left with the Night Sister to inject. A special list hung in the operating theatre on which was written, by the surgeon in charge of the case, the name of any patient for whom treatment was required to begin that day. This list was inspected at regular intervals by the Transfusion Officer or Orderly. Similarly, this team supervised continuous intravenous penicillin treatment and local instillations.

LIMITATIONS OF PENICILLIN

The indication from the laboratory that penicillin would have no effect in certain conditions has been confirmed in the field. It has no effect in the following conditions :—

1. When infection is due to *resistant organisms*, such as pyocyaneus, proteus, coliform, and dysenteric organisms, and others shown *in vitro* to be unaffected by penicillin.

2. In about 5 *per cent of staphylococcal infections*. So far no resistant streptococci or clostridia have been encountered. It is probable that the resistance of these staphylococci is an inherent one ; there has been no evidence from work on war wounds that a susceptible organism has been rendered insusceptible by inadequate dosage.

3. Against *susceptible organisms* in necrotic soft tissue and necrotic bone, and in the centre of abscesses and masses of fibrino-purulent material.

4. Against *bacterial toxins*, especially in gas gangrene.

In war wounds Gram-negative infection is not prevented and may appear to be promoted. It is almost invariable for Gram-negative pus to collect in any dead space in a wound when penicillin is systemically administered or locally instilled. Any Gram-negative organisms present in the wound, or introduced from without, appear to multiply with unusual rapidity in the absence of Gram-positive organisms.

Gram-negative infection of a wound has little ill effect, either general or local, and usually disappears spontaneously in a few days, provided there is free drainage from the dead space. There is no evidence that it has any invasive quality in a war wound, though the rare chance of a Gram-negative septicæmia should be remembered. The ill effects of the Gram-positive pus are : (*a*) it is a potential medium for Gram-positive invaders, and (*b*) it may slightly delay healing of the wound by moistening the dressings. Apart from this aspect, penicillin does not decelerate in any way the healing of wounds or bones.

MISUSES OF PENICILLIN

Apart from its accepted limitations, penicillin can be further reduced in value by actual misuse. It is fair to say that most of the many surgeons who have been using penicillin in the treatment of the wounded in Italy have been doing so well. There was, fortunately, little tendency to neglect proper surgery and rely too much on penicillin ; and there was an increasing realization of the need for sustained treatment, and the opportunity of carrying it out with increasing supplies.

Nevertheless, there were many instances of misuse. Patently inadequate doses of penicillin were sometimes given (through shortage of supply or ignorance), and the success or failure attributed to penicillin. Every case, even though it has had only a single insufflation of powder several weeks before, is regarded by all and sundry as a " penicillin case " ; the wise observers accept the fact that any transient effect has by this time worn off, but the ignorant feel that the magic wand has been cast and that is sufficient. To err on the other side and overdose is a good fault, though the surgeon should guard against the tendency to go on giving penicillin hopefully over a long period instead of making a full surgical re-assessment of the case.

The two main causes of misuse are, first, lack of appreciation of the properties of the drug ; and secondly, the lack of proper supervision in the sustained administration. The known properties of penicillin have frequently not been respected—its selectivity for certain organisms only, its mode

of action, its inactivation by other antiseptics, the need for making up fresh solutions, and similar neglects. I have seen it used with inevitably disappointing results in what was obviously a coliform infection; seen it being administered intravenously for days on end in cases of meningitis to which it can gain access in only small quantities by that route; seen liberal use of hydrogen peroxide and eusol in combination with local penicillin; and eye-drops being patiently instilled one month after that solution must have lost all potency. Used intelligently, penicillin can effect most striking and certain changes in the bacterial flora of a wound, but without strict knowledge of the rules of the game it can be quite valueless and may encourage a false sense of security.

The proper supervision entails making a definite team in each hospital responsible for actually giving the drug, and ensuring that they are informed of the commencing treatment. Unless this is done it is not difficult for the patient to miss a repeated 3-hourly injection or fail to have solution instilled down a tube at proper intervals. I have seen intramuscular doses left with a busy Ward Sister to inject and the regular dosage omitted because of the prime need to serve the dinners. I have seen a man die from gas gangrene through neglect of instillations: this particular death could not be attributed to the drug, nor to the false security that allowed the surgeon to suture the wound, but was essentially due to failure of the surgeon to pass on instruction for instillation to the medical officer in the ward.

Many of the faults that have been encountered are peculiar to penicillin, but some, of course, are inherent in the whole of medicine. Concentration on the new field of interest may blind the observer to other lesions present, and I have seen death from septicæmia through such fault: the penicillin-treated leg wound was uninflamed and therefore all was well and the raised temperature could be discounted; the septic area at a transfusion site was neglected.

Penicillin will soon be in very large supply indeed. The fact that as a drug it is innocuous to the patient has very great advantages in general use, but will inevitably lead to careless use. Medical men throughout the world are anxious that this should be minimized. So far in its history the drug has been well controlled, and the Medical Research Council, the Army Medical Service, and the Ministry of Health in Britain and the corresponding bodies in the Dominions and America, have done valuable service, and will continue to do so, by exercising careful supervision in the development of penicillin therapy in general and its application to war surgery in particular.

I am grateful to Sir Howard Florey, Major K. G. W. Saunders, and Major Scott Thomson for photography, and Mr. H. Axtell for preparing photographs from a film taken by Professor Florey.

THE BACTERIOLOGICAL EXAMINATION OF WOUNDS TREATED WITH PENICILLIN

By SCOTT THOMSON, Major, R.A.M.C.

The following report relates to two entirely different series of wounds, viz.: (1) Chronic septic wounds from three weeks to four months old, specially selected because of their refractory sepsis, but not selected because of their bacterial flora; (2) Wounds mostly three to twelve days old arriving unsutured at a general hospital. These wounds had mostly been dealt with surgically in the Forward Area (general débridement and excision). The wounds were not selected because of any apparent presence or absence of suppuration. The patients with chronic sepsis were troops of the First Army who had been in North Africa for a few months only and who were wounded in the spring. The wounded examined at an early stage were troops of the Eighth Army who had been in Africa for over a year and who were wounded in the summer.

METHOD

Series 1

(Chronic Sepsis—57 Wounds)

Specimens were examined daily for two weeks and on alternate days thereafter. Films were made with a loop at the bedside and the following culture media were inoculated from swabs: (1) Blood-agar plate, (2) Robertson's meat medium, (3) Hoyle's medium, (4) MacConkey's medium. Two specimens taken on different days before therapy was begun were inoculated into all of these media, but the daily specimens thereafter were inoculated on to blood-agar plates while the other media were inoculated at frequent intervals.

Series 2

(Early Unsutured Wounds)

In these series the same culture media were used. A single swab specimen was examined and the submission of further specimens to the laboratory was determined by the future progress of the wound.

All strains of staphylococci reported upon were isolated in pure culture and examined for production of pigment and coagulase. All strains of hæmolytic streptococci were examined for production of a soluble hæmolysin. All strains of diphtheroids were examined by fermentation tests.

The above tests for precise identification were considered to be essential, especially in the early wounds, many of which were infected by, but apparently not yet in a state of overt disease because of, virulent bacteria. The colonies of pyogenic cocci were often few in number on the culture plate and in the minority when compared with those of other bacteria (especially 'coliforms'). Under these conditions precise identification is essential. Diphtheroids were studied because of the possibility of a wound infection by a true *Corynebacterium diphtheriæ* in a warm climate.

All strains of pyogenic cocci were tested for susceptibility to penicillin.

RESULTS

Series 1
(*Chronic Sepsis*—57 *Wounds*)

The results are presented in the form of a table which shows the bacteria isolated during the whole of the period of treatment and which of these were not isolated at the outset, but made their appearance at a later date. (*Table I.*)

Table I.—Bacteriological Findings in 57 Wounds with Chronic Sepsis

Bacterium	Total Number	Number in which the Bacterium was not Found at the Outset
Hæmolytic streptococci	41	1
Staph. aureus	33	1
Diphtheroids	37	5
Ps. pyocyanea	32	15
'B. coli'	27	12
Proteus	30	14
γ strep.	14	6
Str. viridans	1	—

Under the title *Staph. aureus* have been entered two strains of coagulase-positive *Staph. albus*. 'B. coli' includes many *aerogenes* strains.

Hæmolytic streptococci were present in the majority of the wounds, and in the majority of 19 wounds from which both hæmolytic streptococci and *Staph. aureus* were isolated, the streptococci appeared to predominate. This was found both in film and culture.

As a wound improved under treatment with penicillin the pyogenic cocci disappeared much more quickly than did Gram-negative bacilli, which often persisted until the wound was completely healed over. In many wounds Gram-negative bacilli made their appearance during treatment. This was particularly true of *Ps. pyocyanea*, which usually persisted until healing was complete.

There were marked changes in the films of pus from wounds as they improved. The pus cells lost their degenerate appearance and many showed very active phagocytosis of pyogenic cocci. Macrophages appeared in increasing numbers and these cells also showed ingestion of large numbers of cocci. The simple examination of the stained film, therefore, was given considerable attention.

All strains of hæmolytic streptococci isolated from wounds of this series were sensitive to penicillin.

Four strains of *Staph. aureus* were found to be insensitive by the *in vitro* test, but there was no correlation between this and the clinical progress of the wound.

None of the strains of corynebacteria isolated was a true *C. diphtheriæ* and only one was morphologically identical with *C. diphtheriæ*.

Series 2 *A*. *Recent Wounds*
(85 *Wounds mostly* 3–12 *days old, but some older*)

Table II shows the results obtained in 85 wounds which had received no penicillin in the Forward Area. These wounds had been excised and dressed (usually with one of the sulphonamides) in the Forward Area. The table shows also a subdivision of the wounds into flesh wounds and fractures.

Table II.—Bacteriological Findings in 85 Wounds 3–12 days Old upon arrival Unsutured at a General Hospital

Bacterium	Flesh Wounds	Fractures	Total
	58	27	85
Staph. aureus	33	13	46
Hæmolytic streptococci	5	4	9

(In another 100 wounds—control series and head injuries, etc.—similar results were obtained.)

From more than half of the recent wounds, therefore, *Staph. aureus* was isolated and identified. This organism was found in flesh wounds and fractures alike. Hæmolytic streptococci were isolated from 9 wounds, but in only 3 instances were they found in the absence of *Staph. aureus*.

Pyogenic cocci were isolated from 57 per cent of wounds at a single swab examination. Although this percentage is large, it is felt that the true result is probably appreciably greater. It was not possible at the time, owing to pressure of work, to examine multiple specimens from a wound.

Series 2 *B*. *Recent Wounds*
(61 *Wounds previously treated with penicillin in the Forward Area*)

These wounds were admitted to the same general hospital from the same campaign as those of Series 2 *A*. The wounds were of the same age group and were examined by precisely the same methods, as specimens from both series were examined in the laboratory at the same time.

Table III.—Bacteriological Findings in 61 Wounds dressed with Penicillin in the Forward Area

Bacterium	Number	Percentage
Staph. aureus	14	23
Hæmolytic streptococci	4	7

There were seven fractures in this series.

There was a marked difference, therefore, in the results of the examination of wounds at this stage, depending upon whether or not penicillin had been used in the Forward Area. The two groups are compared as follows :—

	Penicillin Cases	*No Penicillin*
Pyogenic cocci	26 per cent	57 per cent

The difference exceeds three times the standard error.

It was noticed also that there appeared to be quantitative differences in the richness of the cultures of pyogenic cocci isolated from the two groups, the penicillin-treated wounds yielding very few colonies as a rule on the culture plate.

As a further index of the bacteriological cleanliness of wounds arriving at the general hospital after being treated with penicillin in the Forward Area, the number of wounds yielding *no growth* on *solid* culture media (blood-agar, Hoyle's medium, MacConkey's medium) was recorded. The results of film examinations were not considered satisfactory for this purpose, as most of the wounds had a dry surface.

	No Penicillin previously— 85 Wounds	*Penicillin previously— 61 Wounds*
Number showing no growth on solid culture media	13 (15 per cent)	26 (42 per cent)

All of the strains of hæmolytic streptococci isolated from these early wounds were sensitive to penicillin. Four strains of *Staph. aureus* were found to be insensitive. There was no apparent correlation between this finding and the clinical progress of the wound. Diphtheroids were rarely encountered in the early wounds (14 per cent). 'B. coli' was found frequently, and *Ps. pyocyanea* was also commonly present.

Specimens for bacteriological examination were taken by Major MacLennan in the Forward Area from 59 out of the 61 wounds summarized in *Table III*. His methods were as follows :—

1. Swabs were taken from each wound before and immediately after débridement and heavily inoculated into tubes of Robertson's cooked meat medium.

2. At the same time films were made from each swab and stained by Gram's method.

3. After 48 hours' incubation the meat-broth cultures were examined under the microscope.

4. If streptococci were present blood-agar plates were inoculated. Further examinations then proceeded on routine lines.

5. Because of the very primitive laboratory facilities, all other examinations were postponed until a return to the Base 14 days later. These also were in no way unusual and require no special comment.

6. In no instance was there any obvious discrepancy between the initial microscopic findings referred to in (3) and the subsequent cultural data.

The following table shows the results of examination of these specimens taken in the Forward Area and specimens taken on admission to the general hospital a few days later.

	Pyogenic Cocci				
	Forward + Hospital +	Forward + Hospital −	Forward − Hospital +	Forward − Hospital −	Total
Number	6	12	9	32	59

Hæmolytic streptococci were recovered from two of the wounds in the Forward Area and from two in the hospital. The term 'pyogenic cocci' in the table is used to include these hæmolytic streptococci.

DISCUSSION

On comparing the results of the two main series, viz., early wounds and chronic sepsis, it is of interest to note how many of the early wounds harboured *Staph. aureus* and how much of the chronic sepsis was due to the hæmolytic streptococcus. Many explanations could be advanced to account for this.

1. Although *Staph. aureus* is present in a large number of wounds at an early stage, it does not usually produce a state of overt disease which becomes chronic sepsis.

2. Hæmolytic streptococci are present in a small percentage of wounds even at an early stage. These may be the wounds which progress to chronic sepsis—i.e., there would be a selection of these cases in the Base hospitals after an interval of months.

3. Chemotherapeutic measures already in current use in the Forward Areas may be more effective against the streptococci than against the staphylococci.

4. Hæmolytic streptococci responsible for chronic sepsis may get into wounds at a later stage (? droplet infection or mechanical contamination during wound dressing) and give rise to established and chronic sepsis.

5. Staphylococci may gain access to the wound at a very early stage from the skin of the patient or attendant, while hæmolytic streptococci may gain access to a wound by droplet infection. There is still surprisingly little good evidence upon this important problem.

6. These *comparative* results might not be obtained in another theatre of war. The patients with chronic sepsis were troops of the First Army, who had been in Africa only a few months and were wounded in the spring. The patients with recent wounds were troops of the Eighth Army who had been in Africa for over a year and were wounded in the summer.

There are epidemiological reasons why the carrier rate of hæmolytic streptococci might have been higher in the former group than in the latter—viz., the season of the year, and the length of time the soldiers had been in a hot climate.

THE TREATMENT OF FLESH WOUNDS BY EARLY SECONDARY SUTURE AND PENICILLIN

By F. H. BENTLEY, Lieut.-Colonel, R.A.M.C.
FROM THE SURGICAL DIVISION OF A GENERAL HOSPITAL, C.M.F.

Flesh wounds comprise an important section of the injuries of war, because of their number and because they are readily capable of repair. Given adequate treatment, a high proportion of casualties with soft-tissue injuries can be returned early to full active service.

The only way to obtain early healing of these wounds is by suture. Healing by granulation is slow and the quality of result not high. The problem in wound suture, if mechanical conditions are suitable, is infection. It is in the control of wound infection that penicillin has one of its most valuable roles in war surgery.

This report describes the treatment of 200 consecutive cases of flesh wounds received from Casualty Clearing Stations in Italy during the first week after wounding, and treated by early secondary suture (late primary suture), i.e., suture within the first two weeks (usually the first seven days) after the wound was received. Only cases with an adequacy of skin for complete or subtotal closure are included, and the only open fractures considered are minor ones where the bony injury did not materially affect the issue.

The flesh wounds described fall into three groups :—

1. Penetrating and through-and-through wounds with deep muscle tracks and extensive muscle laceration (101 cases).
2. Penetrating and tangential wounds with muscle involvement but no deep tracks (43 cases).
3. Superficial wounds of skin and fat (56 cases).

1. PENETRATING AND THROUGH-AND-THROUGH WOUNDS WITH DEEP MUSCLE TRACKS AND LACERATION

(101 *cases*)

This group comprises the major problem. Superficial wounds should always be suturable with high chance of success, whatever method is employed. The problem is the treatment of the deep flesh wound with a long track through lacerated muscle, and penicillin has revolutionized this treatment. Formerly the deep tracks were adequately drained, left to heal in closed plaster, and secondary suture or grafting performed late when the problem was only that of a surface wound. Now, as will be seen, these deep wounds are sewn up with considerable success. The saving of time and increased quality of result from this early healing is remarkable.

It is necessary to mention the treatment these wounds had received at the forward medical unit, Field Surgical Unit, or Casualty Clearing Station. The surface wounds had been opened up, skin and deep fascia incised (not excised), devitalized muscle excised and obvious contamination (battle dress, metallic foreign bodies, etc.) removed, and a dressing of sulphanilamide–vaseline gauze applied. In brief, the wound had been cleaned, decompressed, and made safe for the journey to the Forward Base Hospitals. Some wounds had received a powdering with calcium penicillin-sulphathiazole at the Casualty Clearing Station, but this was exceptional. It should be stated here and now that chemotherapy does not replace surgery as the most important factor in wound treatment. Where adequate surgery had been done forward the wound was in excellent shape for suturing. In the unusual case where adequate decompression, etc., had not been done, the condition of the wound on arrival at this level was poor even if the wound had been powdered with sulphanilamide or penicillin, with too much œdema and bulging of unhealthy muscle for suture to be practicable. In such cases further incision had to be followed by a wait of many days before the inflammatory changes subsided sufficiently for suture to be mechanically possible. The stay of these patients in hospital was prolonged.

Similarly at this level the old principles of wound surgery have to be scrupulously followed —avoidance of dead space, tentage, tension. Preparation of healthy skin edges, and accuracy of suture using a plastic technique and fine instruments are essential. It is fair to say that difference in standard of result is obvious between cases where different qualities of technique existed, and wounds will break down though free from pyogenic organisms if the mechanical conditions of the suture are unsound.

Casualties usually arrived on the fourth day after wounding. Oral sulphanilamide had been given as routine since wounding (average dose over the four days was 15 g.), and was discontinued on arrival at this hospital for all cases in this report. If on arrival the limb was comfortable and the patient's condition non-toxic, the wound was not disturbed and the patient was given 18–24 hours' rest, fluids, and general attention. The journey, though expeditious, was always exhausting, and this period of general treatment was valuable. Next day the man was taken to the theatre and the wounds examined. There is nothing to be gained and something to lose by examining the wounds in the wards. If time permits, almost all wounds, however trivial, are worth suturing.

The time of wound suture varied from the second to the sixteenth day, the average time being

the sixth day. The technique employed for instillation of sodium penicillin solution followed the teaching of Lieut.-Col. Jeffrey. Under pentothal anæsthesia—supplemented by inhalation anæsthesia if operation was prolonged—the skin around the wound was cleansed and the wound then explored with the finger. If no deep pockets or penetrating tracks existed, the wound was considered suitable for penicillin powder (Group II). If there were such tracks they were fully explored and opened up so that the extent of the problem was apparent and the penicillin solution might readily reach all parts of the wound.

The possibility of suture was demonstrated by pressing together the wound margins; the skin edges were then narrowly (2–3 mm.) excised together with the superficial wound, unless these were perfectly straight and clean, and the wound margins undermined for the minimum distance necessary to ensure approximation. Devitalized and loose tags of muscle were removed, the deep tracks mopped dry, and obvious foreign bodies taken out. No further search was made for any metallic foreign body that was not readily found by the exploring finger.

The wound was now ready for suture. Suitable lengths of fine rubber tubing (4 mm. diameter) for subsequent instillation of penicillin solution were introduced through stab incisions made at least 1 in. away from the wound margin, and secured by a stitch. The number depended on the size of the wound, extent of deep laceration, and wound infectivity. A wound 8 in. × 3 in. with deep tracks would require two tubes into the wound recesses and one tube into the superficial wound gutter. A through-and-through wound of the limb would need one tube into the track and one into the wound gutter at both entry and exit wounds. If there was a deep potential cavity, the tube into it was sited so that it would act equally as a drain, through which the cavity could be aspirated at each subsequent treatment in the ward. The skin was then closed by approximation with interrupted silkworm-gut sutures. A considerable degree of tension could be safely employed, since under treatment with penicillin œdema is quick to subside, but extreme tension was dangerous—as always—and tight skin-flaps stretched over a hollow in the tissues (' tentage ') were certain to break down at this point. Where tentage occurred the answer was either to rotate a flap of skin and fat to complete the suture, or, if this was impracticable, to leave the wound open at this point and to complete healing with 2 or 3 pinch grafts in 10–14 days' time, when the hollow had filled in with granulation up to skin level.

A bulky dry dressing was secured with firm flannel bandaging, the rubber tubes protruding for 2 in. through the dressings, and penicillin solution instilled down each tube, using a freshly boiled glass syringe rinsed in sterile distilled water. While the tubes were digitally compressed the wound region was gently massaged through the dressings to cause the solution to spread throughout the wound spaces. The tubes were then kinked over a sterile swab laid on the bandaged limb, covered by another swab, and the whole fastened down with strapping.

The patient was nursed so as not to lie on the wounds, and the part immobilized by plaster bandages, splints, or towels, pillows, and sandbags, for the next week.

Aspiration of the tubes followed by instillation of sodium penicillin solution was done morning and evening for the next five days. After the first time instillation rarely caused any discomfort. The sixth day was a 'rest' day, and on the seventh the dressings were taken down and the tubes removed. A discharge of Gram-negative pus was usual from the tube track and sometimes from the suture holes, though with better knowledge of the method this latter became less frequent. Dry dressings were repeated at 1-2 day intervals when any Gram-negative pus was expressed. It is important to keep these wounds dry, since the Gram-negative pus tends to make the suture line moist and increases the cutting in of the sutures. Complete union can be lost at this time by inattention to these details. By the tenth day after operation the suture lines were dry and the wound ' solid '. Sutures were removed on the twelfth day. Until then the limb was kept at rest, but now active exercises were begun and the process of rehabilitation started.

Dosage of Penicillin.—Dosage is a compromise between the minimum volume of penicillin solution needed to reach all parts of the wound and the number of penicillin units necessary to insure wound sterility. Too much fluid makes the wound unduly moist and increases the discharge of Gram-negative pus, with tendency to necrosis at the suture holes; too little solution may leave the wound with pyogenic organisms, and consequent breakdown.

As an example, in a large wound with three tubes, 5 c.c. of sodium penicillin solution (500 units per c.c.) were introduced by each tube at the end of operation, and 3 c.c. per tube given twice daily for the five days of treatment. That is, 15 c.c into the wound to start with and subsequently 9 c.c. twice a day for five days, a total of 105 c.c.—52,500 units.

Our experiences suggest that a moderate-sized surface wound, say 3 in. × 2 in. with a deep track 3 in. long, needs a minimum of 20,000–25,000 units for safety, and larger wounds more in proportion. If the wound space is small, so that the necessary volume of solution for this dosage seems excessive, it might be well to increase the strength of the solution from 500 to 1000 units per c.c..

Presumably equally as satisfactory results as those described below would be obtained if penicillin was administered parenterally (intravenous or intramuscular injection). A few cases of multiple wounds have already been treated in this latter way, but the series is as yet too small for comparison. Two conditions are already clear,

however: the first, that local instillation is much more economical of penicillin; and secondly, that the patients much prefer local instillation, which is completely comfortable, to the three-hourly intramuscular injections, which are painful and often dreaded. It is difficult to persuade some to accept what Professor Garrod has described as "the price of success".

Types of Wound.—A total of 101 cases with 132 separate wounds were treated in this way. The wounds tended to fall into two main types, perforating (through-and-through) wounds, and penetrating wounds.

Twenty-four cases had a *through-and-through limb* wound as their chief injury. The largest wound was one of the thigh where a shell fragment had passed from side to side just behind the femur, an 8-in. track connecting entry and exit wounds 6 in. × 3 in. and 6 in. × 2 in. respectively. The smallest was a mortar wound of the forearm, with entry and exit wounds each 2 in. × 1 in., the 3-in. connecting track passing between radius and ulna. These wounds showed well the explosive effects of a high velocity missile. Although the missile had usually passed straight through the limb, muscle bellies were torn, often inside intact sheaths, for an inch or two surrounding the track, and there was hæmorrhage into the muscles for another two or three inches; intermuscular planes were split open for several inches, with blood-clot lying in the interstices, the injured part presenting an excellent medium for the development of infection and deep sepsis.

The other main type of injury was the *penetrating wound*, often with a wide skin gape. The muscle bordering the track sometimes had a burned appearance and was of leathery consistency. The same explosive effects were seen, and laceration of muscle was a marked feature of these wounds, the tissues being split by multiple fissures so that it was at times difficult to be certain which was the track of the missile. The importance of the penicillin solution spreading throughout these fissures and crevices will be apparent. Seventy-seven cases had penetrating wounds, the average deep penetration being about 5 in. The largest injury was a grenade wound of the thigh, the surface wound 9 in. by 4 in., leading to a track at least 6 in. long, going from mid-thigh up to the pelvis. X-ray examination showed the grenade fragment to be in the vicinity of the ischial spine. This foreign body was not removed, in accordance with our usual practice; the majority of penetrating wounds were left with deep foreign bodies in situ and in only one instance (discussed below) was healing interfered with.

The injuries were frequently multiple. One man had received major flesh wounds from a mine explosion; two surgeons working simultaneously took two hours to repair the wounds, an example of the immediate labour involved in obtaining this primary healing compared to the former method of sulphanilamide–vaseline gauze and plaster-of-Paris; but all wounds healed by primary union and the man will return to full duties.

Nine cases had associated minor bony injury. In 5 the missile had penetrated the ilium into the pelvis, to be removed extraperitoneally at the Casualty Clearing Station; in 3 as part of the exploration for abdominal mischief; in 2 the foreign body remained. In 4 of these cases healing of the flesh wounds was complete and the men are back at their units. The fifth is discussed below. Two breaches of the cortex of femur and tibia did not interfere with primary wound healing, and in 2 instances of comminuted fracture of the fibula primary healing of flesh and bone followed removal of the foreign body and routine wound suture.

Loss of muscle was a prominent feature of some injuries, particularly of the buttock. It was remarkable to find how quickly movement and strength were regained in the limb in such cases after primary healing of the wound. The answer must be that muscle loss can be compensated for if scar tissue is minimal, which primary healing ensures. Obviously there must be a limit to this compensation, but the process is well illustrated in the following 2 cases:—

Two men, each with a wound 7 in. × 3 in. across the buttock, dividing the fibres of the glutei so that the inferior gluteal artery was torn in one and the sciatic nerve exposed in both. The exposed divided muscle was necrotic, and considerable muscle tissue had to be excised; culture of the muscle showed *Str. hæmolyticus* and *Staph. albus*. Wound suture was followed by primary healing and after two weeks' treatment in the gymnasium the men were discharged to Convalescent Depot on the thirty-ninth day after wounding. Each felt some stiffness still in the buttock, but movements of the hip-joint were full and the men walked without limp.

The majority of the wounds were macroscopically clean at the time of operation, but among the total of 101 cases there were 14 with obvious infection that presented us with a new type of problem—the possibility of wound suture in the presence of established sepsis. In 11, immediate wound suture was possible, and as an illustration a summary of one of the most severely infected cases is given.

March 28.—Patient injured by mortar bomb. Shoulder wound dressed at R.A.P. with sulphanilamide powder. Operation at Casualty Clearing Station after 11 hours. Gross damage to skin and muscle left deltoid region: large foreign bodies removed and damaged muscle excised. Dependent drainage provided. Sulphanilamide vaseline gauze, 32,000 units anti-gas-gangrene serum.

April 7.—Admitted to this hospital. Very toxic. Had had 25 g. sulphanilamide since wounding.

April 9.—*Operation.* Entry wound size 2 in. × 1 in. in posterior axillary fold, the wound through the latissimus dorsi and deltoid, with large exit wound 4 in. × 3 in., over the outer aspect of the shoulder. Extensive destruction of deltoid with damaged sloughing muscle remaining and pus ++. Skin edges necrotic.

Skin edges trimmed, sloughing muscle excised. Possible to close skin defect by construction of skin-flaps. Three penicillin tubes inserted into different parts of wound cavity, and drainage provided through wound in posterior axillary fold.

Bacteriological report on muscle: *Str. hæmolyticus* +++, *Staph. albus* +++, *P. vulgaris* +++. The arm was nursed in abduction, and 61,500 units of penicillin were given into the wound over the next five days.

April 16.—Tubes and drain removed. Suture lines red at places. Holding. *Swab* from track: *P. vulgaris* +++, *B. pyocyaneus* +++.

April 19.—Holding satisfactorily. Some necrosis at suture holes where tension greatest. No inflammation of skin. Patient has developed hæmolytic streptococcal pharyngitis with membrane formation. Again toxic. Course of parenteral penicillin begun.

April 22.—Parenteral course stopped. Throat infection cured. Sutures out from wound; no gape. Slight tension necrosis at suture holes (delayed primary union).

April 27.—Movements begun.

May 17.—Wound sound. 60° abduction at shoulder-joint, can raise arm to right angle and is continuously improving. To Convalescent Depot.

Comment.—The course of parenteral penicillin started on the tenth day after operation obscures the issue to a minor extent. The suture lines were, however, holding well at that time and the man had been so very ill that it was thought essential to control the throat streptococcal infection as quickly as possible. The parenteral penicillin did this most satisfactorily. The case is considered a notable success for the methods employed. Left to clean up in plaster-of-Paris, the shoulder-joint would have been largely immobilized by scar tissue.

Of these 11 cases with grossly infected wounds treated by routine suture there were 9 successes and 2 failures. Both these latter were associated with inadequate dosage of penicillin and will be discussed below.

The three infected cases where immediate suture was impossible are instructive, for cases of this sort will be met with in any large series of flesh wounds. A case summary of one can be taken as typical of all three, so far as conditions of wound and treatment are concerned.

March 14.—Wounded by H.E. Dressed with sulphanilamide powder at M.D.S. Operation at Casualty Clearing Station after nine hours; "large wound of hip incised, foreign bodies not found. Sulphanilamide–vaseline gauze."

March 17.—Admitted this hospital. Had had 10 g. sulphanilamide since wounding.

March 18.—*Operation.* Whole thigh swollen. Wound 3½ in. × 2½ in. above right great trochanter, with hæmorrhagic tense muscle bulging through 2-in. incision in fascia lata. Track leads down to and penetrates ilium. Much deep blood-clot. Bulging muscle not contractile.

Free incision of skin and fascia lata; doubtful muscle excised. One penicillin tube to depths of track. Vaseline gauze. Occlusive dressing.

Bacteriological report of muscle: *Aerobic*, heavy growth *M. tetragenus*; *Anaerobic*, unidentified spore-bearing anaerobes.

20,000 units of penicillin were given by the tube over the next four days.

March 22.—Wound less tense. Tube removed. Penicillin powder insufflated into all crevices. Suture of the relief incisions in the skin.

Wound Swab: *Aerobic, Staph. albus, B. coli, Str. viridans*; *Anaerobic*, nil.

Penicillin powder insufflated daily for the next five days.

March 27.—Œdema much less. Subtotal wound suture, 1-in. gape left to avoid tentage above great trochanter.

April 15.—Primary healing of sutured portion.

April 27.—Pinch graft to granulations of small unsutured length.

May 7.—Fully healed. To get up. Start exercises in 4 days.

May 19.—Wound sound. Walks well. Sent to Convalescent Depot.

Comment.—The inadequacy of primary treatment set up a dangerous state in the limb and considerably delayed wound suture. The man was 67 days between wounding and discharge to Convalescent Depot. This type of case illustrates well the principle that successful late primary suture depends in the first place on correct surgery at the forward unit.

Form of Suture.—

	Cases
Complete wound suture	88
Subtotal wound suture (i.e., a gap left of not more than 1 in. in the length of the suture line to avoid tentage or extreme tension)	10
Suture performed late, after preliminary wound treatment, decompression, etc.	3
Total	101

Wound Bacteriology.—Before proceeding to discuss the final results, it will be of interest to consider the bacteriology of the wounds in so far as it affects these figures.

It will be recalled that of the 101 cases, 3 were unsuitable for immediate suture. Of the remaining 98 sutured immediately, swabs were taken of the wounds of 65. As the series progressed it became apparent that when a wound looked perfectly clean it was unusual for any pathogenic organisms to be reported. Since there was already considerable pressure on the hospital laboratory, swabs were not taken from clean wounds in the latter part of the series, but only when the appearance of the wound was not completely satisfactory. If a swab was taken at operation, a second swab was taken at the end of seven days, when the penicillin tubes were removed, by inserting a swab down the tube track into the wound cavity. It is obvious that the significant bacteriology of a wound may not be determined by a wound swab, for organisms may lurk in crevices not explored, but, so far as the limitations of the method permit, the findings are of interest in the alteration in bacteriological flora following penicillin instillation, and in the influence this had on wound healing (*Table I*).

It will be seen from the table that staphylococci or streptococci developed or persisted in the wounds of 13 cases. No wound breakdown occurred in the 52 cases where these organisms

were shown to be absent at the end of penicillin treatment. In the 13 cases where these pyogenic organisms were present only 2 achieved quiescent consequence of primary healing was seen in the quality of the result and in the length of time the men were under treatment.

Table I.—Bacteriology of 65 Wounds before and after Penicillin Instillation

Bacteriology				Union		
At Operation	Number	Seventh Day after Operation	Number	Primary	Delayed Primary	Failure
Diphtheroids	6	Sterile, or diphtheroids, or *B. pyocyaneus*	6	5	1	—
B. pyocyaneus and *B. coli*	1	*B. pyocycaneus*	1	1	—	—
Cl. welchii and *septique*	2	*B. pyocyaneus* and *P. vulgaris*	2	2	—	—
Sterile	19	*B. pyocyaneus*	16	16	—	—
		P. vulgaris and *proteus*	1	1	—	—
		Staph. aureus and *Str. hæmolyticus*	2	—	—	2
Staphylococci and Streptococci	37	*B. pyocyaneus*, or diphtheroids, or *P. vulgaris*	26	24	2	—
		Staphylococci or streptococci persisting	11	2	4	5

healing, 4 held without gape though showing redness, and 7 had varying degrees of breakdown to be classified as failures. They will be discussed below.

As there were only 8 failures in the series (the eighth associated with the presence of a deep foreign body), the importance of the control of staphylococci and streptococci by adequate dosage of penicillin is plain.

Complications.—The only complication developing in this series were 2 cases of small pulmonary infarcts, and 3 recrudescences of old malaria. Apart from one man who died of his wounds two days after admission, a feature of these cases was the complete freedom from anxiety and absence of wound toxæmia once the wounds were sutured and the penicillin treatment was under way.

RESULTS

In assessing the results the following terms are employed :—

Primary Union: *Complete sutures*, quiescent wound healing with no signs of inflammation. *Subtotal sutures*, quiescent wound healing of sutured portion, successful pinch graft later of small unsutured length.

Delayed Primary Union: Some redness at the suture lines, cutting in of sutures, and sometimes necrosis at the suture holes, tension, but no gape of the suture line, the wound remaining totally united.

Failure: Any gape of a suture line.

The different conditions of the wounds have been described at some length in order that the different sorts of problems occurring in these injuries might be apparent. *Table II* gives the results obtained in the total of 101 cases.

Successful Union.—Ninety-one per cent success is a testimony to the efficacy of the method for this difficult type of problem. The

The majority of the cases were transferred to the Convalescent Depot for further exercises and rehabilitation. At the time of transfer the men had had 1–2 weeks' exercises under the care of our Physiotherapy Department, all wounds

Table II.—Results of Suture of Deep Wounds

	Cases	
Primary union	83	
Delayed primary union	9	
		92
Failures		8
Deaths		1
Total		101

were soundly united and ' solid ', the scars linear and level with the skin surface, and the limb free from tenderness. There was some residual stiffness not yet fully worked out, but all cases were expected to regain full mobility.

	Cases	Total
To Convalescent Depot	83	
To unit direct	3	
To United Kingdom for other injuries (amputations, compound fractures, eye injuries)	6	
		92

The patient under treatment the shortest time was a Commando Officer with a mortar wound of the flexor muscles just below the elbow, 3 in. × 2 in., with division of the flexor mass to a depth of 1½ in., just missing the ulnar nerve. The officer was back at the beach-head with his Commandos on the nineteenth day after wounding, with full return of function. He has since written saying the arm is quite normal.

The longest case was that reported above with a wound above the great trochanter that could not be sutured immediately because of the dangerous state of the limb, and that took 67 days before being fit for discharge to Convalescent Depot. There were several 'long-term' disposals as a result of other conditions—50 days (compound fracture radius), 61 days (blast injury lung), 42 days (3 cases of recurrent malaria). The majority of the cases, however, were on exercises by the end of the third week, and the average time from wounding to transfer to Convalescent Depot for the 83 men was 32 days. When each man was discharged an estimate was made of the length of treatment he would need at the Depot. Some would only need a week to accustom themselves to uniform, equipment, and the absence of a spring mattress. The ordinary case with full movement but with a feeling of stiffness was expected to require two weeks, the unusual or protracted cases three to four weeks to regain full fitness. All were expected to be fit again for A1 duties. Taking this estimate, the *average period from wounding to return to unit* of the 86 men (3 returned to unit direct, 83 via Convalescent Depot) is 45 days.

The short time under treatment and the high quality of result are stressed because, it is suggested, these results were not possible before primary suture of deep wounds was made feasible by penicillin; and because it is in this type of case that the Army obtains the greatest return of man-power for the outlay expended on penicillin in a theatre of war.

The former statement is substantiated so far as surgery in this Division is concerned. In this campaign before we were supplied with penicillin the principles of treating wounds with deep tracks were to prevent infection by adequate drainage and using sulphanilamide by mouth, and to suture or graft the surface wound when the deep track was healed. The not infrequent development of deep infection precluded all idea in our minds of immediate suture. Forty-two such cases remained in the Division when penicillin first became available for new casualties, and their treatment was completed on the original plan. Thirty-two of the wounds were healed satisfactorily in an average time of 61 days, 10 developed deep infection for which operation was needed, and 4 of these were evacuated to U.K. as long-term cases. The quality of the result was not high because of the deep scarring. The following is the discharge note of one of the most difficult cases which did well, a through-and-through wound from gluteal fold to groin, finally healed by secondary suture: "To Convalescent Depot (74 days). Scars thick and adherent, but seem sound. Muscles scarred and stiff. Limps." Further details of these cases are not given because the numbers are not comparable, but the general trend is evident.

Failures.—The 8 failures are significant because they point the way to improved technique and a higher percentage of successes.

In 5 cases the dosage of penicillin was inadequate to remove staphylococci and streptococci from the wounds, and they broke down in part of their length, the average dose being 18,000 units, which was too small for the wounds concerned. None of the organisms was found to be penicillin-resistant, and after several days' insufflation of penicillin powder the wounds were successfully resutured in all 5 cases, and the men discharged to Convalescent Depot, soundly healed, at an average time of 45 days from wounding. They will ultimately be fit for A1 duties. Nevertheless, they count as failures. They should have been successes.

In 1 case, a through-and-through wound of the loin, several pieces of battle dress were removed at operation from the track connecting the two wounds. After suture the wounds healed primarily, but some days afterwards some discharge began from the posterior wound; it is probable that some battle dress still remains and forms the basis for the streptococcal discharge from the wound.

The seventh case proved penicillin-resistant (clinically). A wound, 9 in. × 4 in., across the lumbar region, involving the erector spinæ, was sutured on the fifth day. Wound swab was reported sterile, but after 41,000 units of penicillin had been given into the wound over the next five days, the wound broke down completely, obviously infected, and the swab report was *Staph. aureus* +, *Str. hæmolyticus* +. Penicillin powder was applied daily for four days, when the wound swab was again reported *Staph. aureus* +. Sensitivity tests in the laboratory demonstrated that *in vitro* the *Staph. aureus* was sensitive to penicillin. Accordingly, after several further days' insufflation of penicillin powder the granulating wound was excised on the twenty-eighth day and resutured. Swab from the granulations was returned as *Staph. aureus* (penicillin sensitive!), and again 40,000 units of penicillin were instilled into the wound over the five days. On the seventh day the wound was obviously infected and breaking down, swab report *Staph. aureus* + +, and the defect is now healing by granulation.

The failure is of importance because of divergence between tests *in vitro* for penicillin resistance and the result of penicillin treatment *in vivo*. The wound was never freed from streptococci or staphylococci by what should have been a more than adequate dose of penicillin solution and powder. There was no deep sinus to reinfect the wound. The explanation of the failure remains obscure except that in the wound the infecting staphylococcus remained most obstinately penicillin-resistant.

The eighth failure was in one of the three wounds that was in a dangerous state on arrival, similar in all respects to the case fully described above (p. 135), swollen muscle protruding through a small incision in the fascia lata above the great trochanter (muscle culture, *B. coli* and *Cl. septique*), a track leading through the ilium to a

foreign body close to the fourth lumbar vertebra. 30,000 units of penicillin were given by tube along the track down to the ilium, and subtotal wound suture completed on the twenty-eighth day. The suture line healed normally, but a sinus developed at the unsutured part, presumably in connexion with inadequate sterilization of the track or the retained foreign body.

The one death was a casualty admitted after seven days, very toxic, with a history of 'fits' at the Casualty Clearing Station and presenting extensive wounds of buttocks and thighs (9 in. × 3 in., 7 in. × 4 in., 3 in. × 2 in., deeply involving glutei and hamstring), foul smelling and necrotic. Wound swab, *B. pyocyaneus* and diphtheroids. It was thought that if the wounds were left the man would die of toxæmia. Accordingly, after 24-hours' general treatment, the wounds were cleaned, part sutured, and penicillin instillations begun. In spite of intravenous fluids the man did not improve, and died 24 hours after operation. The post-mortem examination showed nothing more than the flesh wounds, no anaerobes.

2. PENETRATING AND TANGENTIAL WOUNDS WITH MUSCLE INVOLVEMENT BUT NO DEEP TRACKS

(43 *cases*)

When exploration of the wounds showed muscle laceration but failed to reveal a deep track, the wound was considered suitable for the use of penicillin powder. Preparation of the wound for suture was similar to that described in the previous section, but as the depths of the wound could be reached, excision of infected muscle, if the wound was dirty, could always be fairly complete. Routine swabs for wound bacteriology were not taken. It was important to obtain full hæmostasis in order that the powder was not washed away by blood whilst suture was proceeding. A heavy frost of calcium penicillin–sulphathiazole powder (2000 u./g.) was insufflated into all parts of the wound, taking care to reach all crevices and the under aspects of the skin-flaps. The skin was approximated with silkworm-gut sutures, a dry dressing applied with firm bandaging, and the wound kept at rest until the sutures were removed on the tenth day.

Different kinds of wounds were treated in this way. Five were wounds of the back extending into compound fractures of the body of the scapula. One was a large skin defect of the lateral chest wall (9 in. × 4 in.), originally penetrating the pleura, but the pleura and muscle had been sutured at the Casualty Clearing Station. Both pleural cavity and surface wound healed without infection, and the man was discharged to Convalescent Depot with full lung expansion and on graded physical training at 48 days.

The wounds were often multiple, and it is particularly in multiple wounds that this simple method of suture is most useful. One man had five mortar wounds into muscle, varying in size from 2 in. × 1 in. up to 7 in. × 5 in., but all healed primarily and the man left for Convalescent Depot on the thirty-second day.

A useful suture was performed in a casualty who had a shell wound of each thigh just below the gluteal fold, one 5 in. × 2½ in., the other 9 in. × 4 in., dividing the superficial fibres of the hamstrings. Although there was considerable tension on suture of the latter wound, with some consequent necrosis at the suture holes, there was no gape (delayed primary union) and the man was discharged to Convalescent Depot on the thirtieth day after wounding.

Forty-three cases with 55 wounds were sutured; 42 of the cases were straightforward wound sutures and the average size of their wounds was 5 in. × 2 in., extending shallowly into muscle. The forty-third case was different and will be described more fully because it illustrates well the potentialities of the method in the control of infection and the solution of a difficult and not uncommon problem.

March 31.—Injured by mortar bomb. Two small penetrating wounds posterior calf, with injury of posterior tibial vessels. *Operation* at Casualty Clearing Station after 10 hours. Calf very tense; vertical incision (no skin excision) through skin and calf muscle, posterior tibial vessels tied. Nerve intact. Sulphanilamide–vaseline gauze, plaster-of-Paris.

April 7.—Admitted this hospital. Leg painful. Plaster-of-Paris removed. Whole leg greatly distended and the *incision* of the calf had swollen to gape 10 in. by 4 in. Incision in calf muscles explored, no blood-clot. Muscles clean and contractile. The condition was one of severe œdema of the muscle of the leg. Penicillin powder insufflated into all parts of the wound. Vaseline gauze. Padded plaster-of-Paris.

April 15.—Plaster-of-Paris changed. Œdema greatly reduced, but suture not yet possible. Wound swab, diphtheroids. Penicillin powder insufflated into all parts of the wound. To be repeated daily on to surface wound for three days.

April 18.—Œdema still less. Wound swab, diphtheroids. *Operation*: Surface granulation excised down to muscle. Penicillin powder insufflated. Complete skin suture, under moderate tension. Plaster-of-Psris.

April 29.—Sutures out. Primary union, completely quiescent. Walking. Plaster-of-Paris.

May 9.—Discontinue plaster-of-Paris. Start full exercises.

May 23.—To Convalescent Depot. Linear scar. Walking well. Full movements in knee. Full dorsiflexion ankle. Plantar flexion limited by 10°; should soon be complete.

Comment.—Infection was prevented by penicillin/sulphathiazole powder, while severe traumatic œdema subsided over a period of 18 days, sufficiently for suture to be possible. Primary healing. Full functional result obtained.

RESULTS

The results of the series of 43 cases are shown in *Table III*.

The average time from wounding to discharge to Convalescent Depot for these 43 cases was

26 days. All would be fit for return to A1 duties after a further 7–14 days.

Table III.—Results of Suture of Wounds involving Muscle but no Deep Tracks

	Cases	
Primary union	40	
Delayed primary union	2	
		42
Breakdown of ½ in. (tension)		1
Total		43

3. WOUNDS OF SKIN AND FAT
(56 *cases*)

These wounds are of importance only in the time taken before the man is fit to rejoin his unit. In periods of great business, and before the time-saving value of suture of these wounds was fully appreciated, small superficial wounds were usually left to heal on eusol dressings. A check was kept at discharge parade of the length of time taken for superficial wounds of about 1 in. in length to heal. The average of 200 cases was 34 days from wounding to the time the man was discharged to his unit, much longer than any of the surgeons would have expected from their impression in the ward.

Delayed primary suture, although a trivial procedure, was thus of great time-saving value in these minor cases. A total of 56 cases with 65 wounds, average size 2½ in. × 1 in., were sutured. If the wound was dirty penicillin/sulphathiazole powder was insufflated into the wound daily for three to four days before operation. Otherwise immediate suture was performed after trimming the skin edges and a single insufflation of the powder.

RESULTS

These are shown in *Table IV*.

Table IV.—Results of Suture of Superficial Wounds

	Cases
Primary union	54
Delayed primary union	2
Total	56

The average time from wounding to discharge to duty was 20 days.

SUMMARY OF RESULTS OF THE 200 CONSECUTIVE CASES

From *Table V* it is seen that in a consecutive series of 200 casualties with flesh wounds treated by early secondary suture plus local penicillin, primary healing was obtained in 190, i.e., 95 per cent. Estimated as wounds, there were 252 wounds, with primary healing in 240—again 95 per cent.

Six of the 190 cases with primary healing were sent to U.K. for other injuries. The remaining 184 cases will be returned to A1 duties.

Average period from wounding to return to duty :—

1. Deep wounds (time in hospital, plus estimated time at convalescent depot)	45 days
2. Wounds involving muscle but no deep tracks (time in hospital, plus estimated time at convalescent depot)	36 ,,
3. Superficial wounds	20 ,,
Average for the series	35 ,,

Table V.—Summary of Results of the Whole Series

	Primary Union	Delayed Primary Union	Failure	Death	Total
Deep wounds	83	9	8	1	101
Wounds involving muscle but no deep tracks	40	2	1	—	43
Superficial wounds	54	2	—	—	56
Total	177	13	9	1	200

These wounds were typical of soft-tissue battle injuries, and the results show that in the presence of penicillin wound infection is controlled and that a high proportion of success follows early secondary suture. Wound suppuration should be a rare event in future injuries.

This report represents the work of the whole Division, of Specialists, M.O.'s, and Sisters, who have produced the best team work that could be wished for. It is a pleasure to acknowledge our indebtedness to Lieut.-Col. J. S. Jeffrey, Penicillin Officer, C.M.F., whose teaching and methods of penicillin instillation have been followed; to Brigadier Harold Edwards, Consulting Surgeon, C.M.F., who has stimulated and encouraged this process of suture; and to Col. C. H. K. Smith, O.B.E., M.C., Officer Commanding this General Hospital, who has allowed no difficulty to exist in the work that has been entailed. Special mention must be made of Capt. James Key, Trainee in Surgery, whose painstaking records form the basis of this report.

EARLY CLOSURE OF SOFT TISSUE WOUNDS WITH CHEMOTHERAPEUTIC AGENTS

A COMPARATIVE STUDY OF SULPHANILAMIDE AND PENICILLIN

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THE cases reviewed in this report cover two distinct periods—(*a*) *before* and (*b*) *after* penicillin became available. The operative treatment was carried out by the same surgeon in both periods. The penicillin cases are confined to those sutured up to and including March 31, 1944, which makes the shortest follow-up period six weeks—probably an adequate period to allow for the possibility of subsequent breaking down of wounds. Since that date more penicillin has been available, and every wound has been sutured if apposition is possible.

The wounds have been divided into four series :—

1. Cases selected as suitable for secondary suture by the surgical criteria described below and sutured with sulphanilamide powder (*Table II*).

2. Cases selected in the same manner as those in Series 1 and regarded as comparable to them, but sutured with one insufflation of penicillin-sulphathiazole powder (5000 units per gramme) (*Table III*).

3. Cases which in the pre-penicillin days would have been regarded as quite unsuitable for suture. These were treated with one or more insufflations of penicillin-sulphathiazole powder followed by suture (*Table IV*).

4. A small series of larger and more septic wounds treated by penicillin solution (250 units per c.c.) instilled through rubber tubes introduced into the wound at the time of suture (*Table VI*).

Experience of wounds of soft tissue during the North African campaign had shown that closure of clean and recently excised wounds with or without the insufflation of sulphanilamide powder was followed by a fair measure of early success. In view of the forward position of the hospital it had proved impossible to follow the cases for more than a short period, and the number of cases which ultimately broke down could not be ascertained. In Italy, however, things were very different as the hospital was in a Base area with the Convalescent Depot adjacent to it. Any wound which broke down during rehabilitation was returned to the hospital and so a reliable follow-up could be carried out.

Secondary suture with sulphanilamide had been carried out in all soft-tissue wounds which were considered suitable for closure. The wounds selected were cleanly excised, with no necrotic tissue, with no obvious or only slight sepsis on clinical examination, and with no surrounding induration or tension. The results were very encouraging. With the advent of penicillin it was considered that it would be worth while to select a similar series by the same criteria, to treat them with one insufflation of penicillin-sulphathiazole powder, and to compare the results of suture in the two series. While swabs were taken from some of the wounds, the results of culture were not awaited and suture was performed there and then. The method of selection, therefore, has been clinical or surgical, and not bacteriological. This may seem to be a haphazard method, but the cases were selected and classified in the operating theatre where the first dressings were removed ; stress of work did not permit awaiting bacteriological findings.

Furthermore, during the 'pre-penicillin' period, 240 soft-tissue wounds were admitted, and 71 (just over 29 per cent) were considered suitable for closure. In the penicillin period under review, 417 wounds of soft tissue were admitted and 110 of these (just over 26 per cent) were regarded as comparable with the previous series. It seems likely, therefore, that the similarity is reasonably accurate. During the penicillin period 108 wounds (26 per cent), in which suture would previously have been considered dangerous or impossible, were closed, using one or more insufflations of penicillin-sulphathiazole powder. A further 18 wounds (4·3 per cent) were sutured using the penicillin solution instillation technique through small-bore rubber tubes. In all, therefore, during the penicillin period under review, 56·3 per cent of the soft-tissue wounds were sutured as against 29 per cent in the pre-penicillin period (*Table I*). This number would have been greater had the supply of penicillin allowed.

Table I.—TREATMENT OF SOFT-TISSUE WOUNDS IN RELATION TO PERIOD

PERIOD	TOTAL SOFT-TISSUE WOUNDS ADMITTED	NUMBER OF WOUNDS SUTURED			
		Clean	Septic	Large, very septic	Total
Pre-penicillin	240	71 (29 per cent)	—	—	71 (29 per cent)
Penicillin	417	110 (26 per cent)	108 (26 per cent)	18 (4·3 per cent)	236 (56·3 per cent)

Assessment of Healing.—Previous reports had described three types of result: (1) Complete union; (2) Subtotal union; (3) Complete failure. These did not seem to include all the types of healing encountered, and accordingly healing has been classified into five categories:—

Healing Standard 1.—The wound healed like a clean operation scar, i.e., it was dry and soundly healed with minimal scar tissue when the stitches were removed on the tenth to fourteenth day after suture.

Healing Standard 2.—The wound surface was slightly moist, with serous or sero-purulent discharge, and there was slightly more scar tissue, although the edges were in good apposition when the stitches were removed on the fourteenth day. Complete healing occurred in another few days.

Standards 1 and 2 may be regarded as complete union.

Healing Standard 3.—The wound is comparable to that in Standard 2 but there is up to 1 in. unhealed. This gap would usually heal without further difficulty after a further delay of 10 days or occasionally longer.

Healing Standard 4.—Union of up to half the extent of the wound.

Healing Standard 5.—Over half of the wound broke down. This was regarded as complete failure.

In almost all cases in Standard 4 the unhealed area proved very resistant to treatment and healing was long delayed. For this reason cases in Standards 4 and 5 have been regarded as failures.

Technique of Suture Employed.—Wounds which had been thoroughly excised 10 days or less before suture were cleansed thoroughly with normal saline, any epithelium growing from the skin edge was removed with a sharp knife, the undercutting necessary to secure apposition with minimal tension was carried out, hæmorrhage was controlled by pressure, all areas of the wound were insufflated with a fairly heavy frosting of penicillin-sulphathiazole powder (5000 units per gramme) and the wound was sutured.

Wounds which had been excised over 10 days before suture and wounds in which the primary treatment had been inadequate, were excised thoroughly and then treated as above.

In all cases accessible foreign bodies were removed.

In most cases no attempt was made to suture the fascia, and buried sutures were never used. In some cases the fascia was brought into apposition by deep figure-of-eight skin sutures.

Penicillin solution instillation was employed in the larger dirty wounds which could not be completely excised or where septic cavities or sinuses remained. One or more tubes were inserted through stab incisions and 250 units of calcium-penicillin in distilled water were instilled into each tube twice daily for four days.

Bacteriology.—In the early stages of the investigation swabs were taken at operation and on the fourth or fifth post-operative day. It became apparent almost at once that on the fifth day healing was so secure that it was impossible to take a swab without contact with the skin, and the opening up of the wound would in no way be compensated by the information gained. Thereafter wounds were not dressed after suture until the removal of the stitches on the tenth to fourteenth day, unless the general reaction indicated that inspection of the wound was necessary.

Table II.—Secondary Suture without Penicillin. 'Control' Series with Sulphanilamide

Interval between Primary and Secondary Wound Treatment	Number of Wounds		Healing Standard				
	Clean	With Slight Sepsis	1	2	3	4	5
2–5 days	46	6	22	11	9	1	9
6–10 days	13	3	5	4	2	3	2
Total 10 days and under	59	9	27 (39·7 per cent)	15 (22 per cent)	11 (16·2 per cent)	4 (5·9 per cent)	11 (16·2 per cent)
Over 10 days	1	2	1	1	—	—	1
All cases	60	11	28 (39·4 per cent)	16 (22·5 per cent)	11 (15·5 per cent)	4 (5·7 per cent)	12 (16·9 per cent)

Systemic signs of fever and rise in pulse-rate with pain and swelling locally occurred in 1 case only, and the wound healed in Standard 3.

In general, it may be stated that the bacteriological findings did not always correspond with the clinical features of the wounds and did not give a reliable indication of the probability of successful suture. Wounds with apparently massive infection, with coagulase-positive staphylococci, hæmolytic streptococci, or mixed organisms, might heal well, while clinically dirty wounds in which cultures were found to be sterile sometimes broke down *in toto*.

The presence or absence of such organisms as coagulase-positive staphylococci on the post-operative culture did not seem necessarily to affect the result of the sutures.

RESULTS OF SECONDARY SUTURE

1. Pre-penicillin or 'Control' Series.—In all 71 wounds were sutured using sulphanilamide powder, with 61·9 per cent of satisfactory results. Details are in *Table II* above. The

average stay in hospital after suture in cases without other lesions was 22·7 days.

2. Cases Comparable to the Pre-penicillin Series Closed with One Insufflation of Penicillin-sulphathiazole Powder.—In this series 110 wounds were sutured, with complete success in 103, or 92·9 per cent. The remaining cases were all in Standard 3 and therefore there were no real failures. In cases sutured up to 10 days after primary excision, 96·8 per cent were successful. It is interesting to note that in suture after 10 days a much higher percentage of the successes were in Standard 2. The average stay in hospital of cases sutured less than 11 days after excision was 17·6 days, and on the eleventh day, or later, 24·3 days. It must be remembered that these are the initial cases when experience in the technique had not been gained and more use should have been made of insufflation for 2 days before operation. Some of the cases would, as we now know, have been certainly successful with penicillin instillation, but the small supply of penicillin solution made this impossible and the attempts were made with some remarkable results.

Table III.—Secondary Suture of Wounds Comparable to those in *Table II*: One Insufflation with Penicillin-sulphathiazole powder

Interval between Primary Wound Treatment and Suture	Number of Wounds		Healing Standard				
	Clean	With Slight Sepsis	1	2	3	4	5
3–5 days	21	4	21	3	1	—	—
6–10 days	33	5	34	3	1	—	—
Total 10 days and under	54	9	55 (87·3 per cent)	6 (9·5 per cent)	2 (3·2 per cent)	—	—
11–15 days	14	6	16	2	2	—	—
16–20 days	11	8	16	1	2	—	—
21–40 days	2	6	2	5	1	—	—
Total over 10 days	27	20	34 (72·35 per cent)	8 (17 per cent)	5 (10·65 per cent)	—	—
All cases	81	29	89 (80·2 per cent)	14 (12·7 per cent)	7 (6·4 per cent)	—	—

The average stay in hospital after suture was 24·5 days. Details are in *Tables IV* and *V*.

4. Cases Treated by Intubation and Penicillin Instillation.—This method was employed in only 18 wounds. In 2 cases the dosage of penicillin was inadequate owing to shortage of supplies and they were both failures, one Standard 4, and the other Standard 5. The third failure was a case which was sutured with so much tension that the blood-supply was impaired. The number of cases is small, but the success of a method which at first sight seems to break all the surgical rules of free drainage and wide opening of septic wounds is truly miraculous The results are shown in *Table VI*.

Table IV.—Cases which would not have been sutured before penicillin: 108 Cases, 2 Insufflations before Suture, others as in *Table III*

Interval between Primary Wound Treatment and Suture	Number of Wounds		Healing Standard				
	Sepsis +	Sepsis ++	1	2	3	4	5
3–5 days	2	—	—	—	1	1	—
6–10 days	26	7	17	8	2	4	2
Total 10 days and under	28	7	17 (48·6 per cent)	8 (22·9 per cent)	3 (8·6 per cent)	5 (14·2 per cent)	2 (5·7 per cent)
11–15 days	19	9	23	2	1	2	0
16–20 days	8	7	5	5	1	3	1
Over 20 days	24	6	13	4	7	5	1
Total over 10 days	51	22	41 (56·2 per cent)	11 (15·1 per cent)	9 (12·3 per cent)	10 (13·7 per cent)	2 (2·7 per cent)
Total all wounds	79	29	58 (53·7 per cent)	19 (17·6 per cent)	12 (11·1 per cent)	15 (13·9 per cent)	4 (3·7 per cent)

It seems reasonable, therefore, to aim at closing clean wounds before 10 days after primary excision. Detailed statistics are in *Table III*.

3. Septic Soft-tissue Wounds which would not have been Sutured in the Pre-penicillin Period.—In this series 108 wounds were sutured. With suture up to the tenth day after primary treatment, there were 19·9 per cent failures, and over 10 days 16·4 per cent were not successful.

An attempt to use sulphathiazole emulsion in an exactly similar way by instillation through rubber tubes as a control was tried. It was abandoned because the first case developed such severe systemic signs of sepsis that the stitches had to be removed on the third day and the wound left widely open.

Table V.—Days in Hospital after Suture

Time of Suture	Cases in Table II	Cases in Table III	Cases in Table IV
Under 11 days	22·7	17·6	22·8
Over 10 days	—	24·3	25·4
All cases	—	21·0	24·5

CONCLUSIONS

While the cases are insufficient in number to warrant the laying down of definite rules, the following tentative conclusions may be drawn :—

1. If the wounds are clinically clean they should be sutured early, preferably before ten days.

2. If the wound is infected by clinical standards it should be insufflated with penicillin for two days before suture. The value of this technique was not fully appreciated in the early cases and it should have been employed more frequently.

Table VI.—Large Septic Wounds treated by Penicillin Instillation

Time of Suture	Healing Standard				
	1	2	3	4	5
10 days and under	8	—	3	—	—
Over 10 days	2	—	2	1	2
All cases	10	—	5	1	2

3. Provided that drainage of the wound is adequate it is better, in septic wounds, to allow the acute phase to subside and to perform the secondary suture after ten days.

4. No matter how clean a wound may seem ten days or more after primary excision it should be treated as an infected wound.

It must be borne in mind that the success of penicillin in no way condones incomplete or inadequate primary surgical treatment, but it is imperative that this primary treatment should conserve as much skin as possible in order that suture may be readily carried out. The success of penicillin with suture in wounds of the soft tissues has been so dramatic that such cases should be evacuated as soon as possible with their primary operation dressings intact. These dressings should be removed in the theatre in order that they may all come under review by the surgeon, and all wounds (no matter how small they may be) in which it is possible to secure good apposition should be sutured. Furthermore, when complete apposition is impossible in large wounds the period of incapacity will be greatly shortened by partial suture and the early grafting of the unhealed area.

The scars resulting from secondary suture have been satisfactory, and in only a very small minority of the cases have they been adherent to the deeper tissues. In our experience they have been infinitely better than those resulting from healing by granulation and are much less liable to break down later.

SUMMARY

1. 68 wounds were sutured without penicillin, with 23 per cent of failures.

2. 110 comparable wounds were sutured with one insufflation of penicillin-thiazole powder, There were no failures.

3. 108 wounds regarded as unsuitable for suture by pre-penicillin standards were closed with insufflation of penicillin, with 17 per cent of failures.

4. 18 large septic wounds were sutured and treated with instillations of penicillin solution through tubes. There were only 3 failures, each of them attributable to errors of technique.

5. The results are so good and the period of morbidity so lessened that all soft-tissue wounds, however small, should be sutured with the aid of penicillin.

6. Recovery is not only rapid, but the nursing care required and the number of dressings have been greatly lessened, leaving the nursing staff much more time to devote to the more serious cases.

7. Penicillin has in no way replaced and can can never be a substitute for thorough primary surgical treatment.

8. Bacteriology is of little or no value in deciding when and when not to suture. Failure has followed suture of clinically dirty wounds in which the culture was sterile, and success has followed the suture of wounds with apparently massive staphylococcal and streptococcal infection.

9. All soft-tissue wounds should have their first dressing following débridement done in the theatre in order that they may be reviewed by the surgeon. The patient should be prepared for anæsthesia in order that suture may be carried out.

10. The scars resulting from secondary suture are much more supple and less liable to late breaking down than those following healing by granulation.

It is a pleasure to record my grateful thanks to Major J. Goldman for the care and interest he has taken in the extra work entailed in carrying out the bacteriological investigations of these cases.

BATTLE CASUALTY FRACTURES IN ITALY

TREATMENT WITH PENICILLIN

By J. S. JEFFREY, Lieut.-Colonel, R.A.M.C.

The infected compound fracture is one of the most difficult problems that the surgeon of war wounds has to face, while for the patients the illness is long and trying, and not infrequently ends in amputation or death. The penicillin supply position in Italy during January–June, 1944, was such as to allow treatment with penicillin for most of the severe fractures sustained by British and Dominion soldiers in battle. It became the aim to start all such fractures on a systemic course of sodium penicillin within fourteen days of wounding and before infection was chronically established. With its specific action against the pathogenic organisms of compound fractures, penicillin can do nothing but good if applied routinely, provided it is accepted simply as an adjunct to proper surgery.

In addition to giving routine penicillin, it was the aim to shut off the fracture from the exterior at the earliest possible moment by suture of the wounds. The conversion of the open fracture into virtually a closed one, by the healing of the wound, is a milestone along the road of treatment of any compound fracture, and particularly the comminuted fractures of war. Comminution of a bone in itself does not delay union, and indeed in a healthy young man appears to speed callus formation even in the presence of mild infection. But if infection becomes rampant among multiple bone fragments, then what might have been a bone-graft becomes a sequestrum, and the results can be disastrous.

TECHNIQUE

In the Forward Areas (Field Surgical Units and Casualty Clearing Stations) the wounds were excised; insufflated with penicillin-sulphathiazole powder; the wounds left open and covered with vaseline gauze; and the fracture immobilized for transport. The powder was at a strength of 5000 units calcium penicillin per gramme of sulphathiazole, and was insufflated to form a thick hoar-frost, the usual amount being 2–4 g. At the Base hospital the wounds were trimmed, if necessary, and partially sutured, leaving the middle of the wound open as a drainage channel. Accessible bone fragments were removed, but only if completely detached. Fractures of the femur were immobilized by skeletal or skin traction and usually a Thomas's splint; other fractures by closed plaster. Thereafter the patient was given a systemic course of sodium penicillin. Initially in our investigation this treatment was started after operation, but latterly better results were obtained by having the patient 'penicillinized' for 24 hours before operation.

The course of penicillin lasted for 5–10 days (500,000 units–1,000,000 units) or longer if necessary; 15,000 units three-hourly intramuscularly for the first three days, thereafter at four-hourly intervals; or in continuous intravenous glucose saline infusion delivering 5000 units per hour. The wounds were left undisturbed for 21 days, and the decision whether to continue penicillin after the 5-day course depended on memory of the degree of wound inflammation at the time of operation and the patient's general condition. After three weeks if the case was not progressing satisfactorily the organism present was tested for sensitivity to penicillin, the wound re-assessed, and drainage improved, and sometimes more penicillin given.

This treatment was carried out so far as possible routinely on all fractured femurs, for they are the commonest serious problem from the infection point of view; and on the worst fractures of tibia, upper end of humerus and shoulder, and pelvis.

RESULTS

Femurs.—Altogether about 150 battle casualty fractures of the femur were treated with penicillin (average 800,000 units). It was evident that serious infection was largely prevented, and this can be seen in the series, with contrasts, reported by Major R. J. Furlong and Major J. M. P. Clark (p. 147).

Similar decreases in mortality and amputation figures were noted at the two other centres where special investigation was undertaken. A certain number of femurs will always require amputation where the bone defect is such that an artificial leg is a better proposition, and when there is a major vascular injury. But certainly few of the patients, if any, should die through sepsis if the organisms they are harbouring are sensitive to penicillin.

Nevertheless, although there was a decrease in major sepsis, about one-quarter of all the penicillin-treated femurs showed signs of persistent minor infection three months after wounding, which is similar to the infection rate in contrast cases that survive to that period. This persistence of infection was due principally to difficulty in maintaining adequate drainage of the Gram-negative pus and autolytic products (and sometimes the frank pus), and to a lesser extent to insufficient penicillin and insensitive strains of staphylococci.

Other Fractures.—Many open fractures of other bones were treated with penicillin, but the results were not studied systematically. In general, they were a simpler problem and ran a more straightforward course than the femurs. The systemic course of penicillin seemed beneficial in most cases and the overall results were

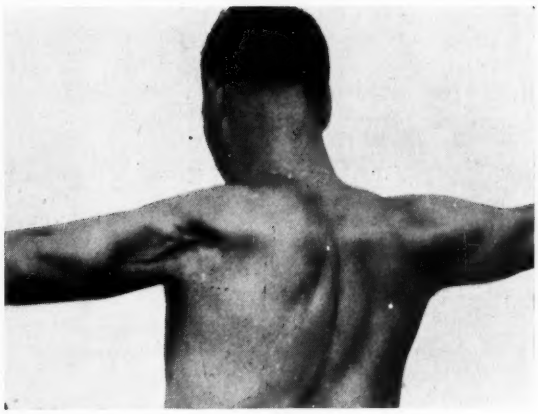
excellent. There were many striking instances of difficult fractures of the pelvis progressing satisfactorily, of early and good shoulder movement in fractures of that region, and other tributes to the value of control of infection. A few fractures were treated successfully with large doses of penicillin locally instilled to the site of fracture and the results were such as to encourage further trial.

The case of *Sgt. S.* (*Fig.* 81) shows the control of infection by penicillin and the advantage of partial suture. A shell fragment had fractured the upper end of humerus (multiple fissuring), and the wound was purulent when excised five days after wounding. In spite of cutting through infected tissue there was no inflammation of the wound six days after operation, and the fracture was already becoming shut off from the exterior. 500,000 units penicillin were given systemically during 5 days following operation.

A

B

C



D

E

FIG. 81.—A, Fractured humerus with skin and muscle loss five days after wounding; immediately before wound excision. *Culture: Staph. aureus*; Clostridia. B, Six days after wound excision and partial suture. *Culture:* Pyocyaneus; Coliforms. C, Six weeks after wounding. Wound firmly healed. D, E, Twelve weeks after wounding. Fracture firmly united. Deltoid loss, but good shoulder movement.

DISCUSSION

The critical points now to be discussed refer to all fractures, though their main bearing is on the commonest problem—the compound fracture of the femur.

Length of Penicillin Course.—Any tendency to underdose is to be deprecated, and on general principles it is better in a severe fracture to give an 8-day course rather than a 5-day course (100,000 units a day, on average). Five days is sufficient in a straightforward case; 8 days may save a doubtful fracture from becoming chronically infected; but when the case requires 14 days and more it is almost certain that the original surgery has been at fault and that infection will recrudesce. (These time-figures refer to fractures beginning treatment within 14 days of wounding; later fractures need a longer course and are more problematic). On the whole, the fractures in Italy did not appear to be underdosed; and when they were it was usually not because of shortage of penicillin supply, but through a desire to save the patient and the busy staff from the need for further constant injections.

Value of Suture.—The failures due to inadequate drainage raised acutely the question whether we were wise to attempt suture of the wounds in these compound fractures. The strong argument in favour of suturing is that it gives support to granulation tissue in shutting off the fracture from the exterior, and that it helps to obliterate dead space. This was frequently confirmed in practice. It is probable, too, that the minimal scarring is an aid to later joint movement. Complete suture was never attempted, but even so it was apparent that partial suture was responsible for damming up pus and debris in some cases. Particularly was this so when the method of splinting necessitated elevation of the lower end of the thigh; then sumping was apt to occur, with the pus gravitating up the thigh. In the light of experience I would suggest that anterior wounds can safely be sutured, but that posterior and main drainage wounds should be sutured only in any part well away from the main drainage channel, which must on no account be occluded.

The maintenance of dependent drainage for the first ten days of treatment is so important that we sometimes inserted large-bore rubber tubes into the wound and down to the fracture site if it was feared that the muscles might come together too quickly. Planned incisions for drainage were only made in a few cases, principally to deal with existing sumping in the upper postero-lateral aspect of the thigh. To ensure drainage from a single anterior wound over femur or knee-joint is a difficult problem, but we found it effective to turn the patient on to his face for several hours each day; the limb was immobilized in a Thomas's splint, with fixed traction and encircling plaster band. With this further appreciation of the importance of drainage, the later results of partial suture and penicillin have been much better.

Bone-plating.—Selected fractures were chosen for onlay of Lane's plates. It need hardly be said that we would never regard plating as a routine procedure, because (*a*) fragmentation of the bone renders most of them unsuitable for plating, (*b*) the results from conservative fracture treatment in young men can be so good, and (*c*) the time period when these compound fractures are dealt with (about 6 days after wounding) is a dangerous one from the infection aspect. The fractures selected for plating were: (1) Those in which attempts to correct malposition had failed; (2) Some in which internal fixation of the femur was likely to make easier the nursing of other wounds; and (3) Some with large wounds that seemed to invite plating without the need for further cutting. The impression gained from plating experience in Italy was that the immediate results were similar to those achieved by conservative methods, and the convalescence easier.

CONCLUSIONS

There is a desire that is wholly praiseworthy on the part of the medical profession that more should not be attempted or expected from penicillin than common sense justifies, and that the pitfalls which attended the introduction of the sulphonamides should be avoided. These experiments with compound fractures are such as had to be done some time. Plating, internal manipulations, suturing—none of these would be legitimate surgery in compound fractures over 12 hours old unless one felt assured that penicillin or some other chemotherapeutic agent would control the infection. This control has very largely been obtained, and it is fair to say that none of these 150 fractured femurs, for example, came to any appreciable harm as a result of these radical procedures, and many of them were distinctly the better. Certain it is that fewer men died or lost their limbs than heretofore.

It is certain also that there is no tendency to delayed bone union when the patient is treated with penicillin; if anything the reverse, for callus was sometimes visible by X-ray as early as three weeks after wounding. A few cases of open fractures treated with penicillin one year ago have been followed up to date, and it is apparent that the bones are firmly united.

In assessing the causes of any improvement that may have occurred, we have to distinguish between what is due to the systemic course of penicillin *per se*, what is due to new procedures such as suture of the wound, and what is due to the special care that cases under investigation receive. All of the many surgeons who worked with penicillin in Italy felt satisfied that the rapid subsidence of inflammation in the wounds could not honestly be attributed to anything but the effect of the drug. It is no longer necessary, in the legal sense, to make a case for penicillin. Granted, then, that infection can be controlled by

penicillin, it remains to decide whether a routine systemic course should be grafted on to existing methods of conservative fracture surgery, or whether more radical surgical procedures can be carried out in addition. From my experience, I would say that in compound fractures partial suture of the wounds on the lines indicated above is to be generally recommended; that the need for bone plating and internal adjustments must be viewed with great caution and be performed, of course, only by surgeons experienced in the technique; and that whatever is done there is an overbearing need for meticulously careful and aseptic surgery.

This was part of a Report submitted to the Director of Pathology, War Office, from the Penicillin Control Unit, C.M.F. I am grateful to Major-General L. T. Poole, D.S.O., M.C., for permission to publish this synopsis.

ON THE USE OF PENICILLIN TO CONTROL INFECTION IN OPEN FRACTURES OF THE FEMUR

INTERIM REPORT

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The present investigation is concerned with the results of treatment of 140 cases of open fracture of the femur; 70 of these cases received sodium penicillin administered by intramuscular injection and the other 70, not having been so treated, were used as controls. Before the investigation was started over 50 of the contrast series were already under treatment and had been so for periods ranging from a few days up to six weeks. All open fractures of the femur arriving at the Centre after the start of the investigation received penicillin provided the time interval between sustaining the injury and the establishment of traction and immobilization did not exceed fourteen days; those that did not satisfy this condition were added to the list of controls. The cases were collected consecutively with no form of selection other than the one condition already cited.

The present account, being an interim report, is necessarily incomplete because the patients are at varying stages of their treatment, but an analysis has been made of such figures as are comparable.

METHOD OF USING PENICILLIN

At the outset the drug was administered by a routine, which, though rigidly adhered to in the earlier cases, was modified later. No form of local instillation of penicillin was used. The dose used in parenteral administration was 15,000 Oxford units in 3 c.c. of normal saline, given intramuscularly every three hours for three days and nights and a similar dose given four-hourly during two subsequent days and nights. This course was started, if possible, twenty-four hours before the application of splintage and traction.

The wounds were partially sutured and an occlusive dressing was applied which was not disturbed for three weeks, even should there be a raised temperature and pulse-rate or a discharge of pus from the wound. When this régime had been followed for over half the series it was thought that insufficient quantities of penicillin were being administered, because in some instances, at the first dressing, there were large amounts of foul pus, and some patients had remained toxic and febrile over the whole period. It was observed that the temperature chart formed a sound guide to the progress of the infection, and it became possible to predict when the pus which was present contained Gram-positive organisms, and when pus had been under tension, and if the drainage had been adequate.

Therefore in the later cases, if the patient had been febrile during four days following operation, penicillin was continued sometimes up to ten days. In one or two instances the course was prolonged even longer. One patient who was receiving intravenous fluid had penicillin administered through the drip, so regulated that his dosage was equal to that of the others, namely at the rate of 5000 units per hour. In none of the patients were any toxic signs found that could be attributed to penicillin itself even when over a million units were given.

BACTERIOLOGY

At the start of the investigation a swab was taken of the wounds at the time that the fractures were reduced and again at the time when the original dressings were changed between the third and fourth week afterwards. It is not possible to compare the flora of the wounds initially and at four weeks in the contrasts with that of the penicillin series, because many of

the controls had already passed four weeks before the investigation began and therefore insufficient figures are available. An analysis of the change in flora during the first four weeks in the wounds treated with penicillin is given.

Original Culture	*Total*	*Four-week Culture*	*Total*
Gram-positive	30	G.N.	20
		G.P.	10
Gram-negative	13	G.N.	4
		G.P.	9
Clostridial infection	21	C.	11
		N.C.	10
No clostridia grown	13	C.	13
Sterile	4	G.N.	2
		G.P.	2

G.P., Gram-positive infection (Streps. and Staphs.). G.N., Gram-negative infection (Coliforms, diphtheroids, *B. pyocyaneus*). C., Clostridial infection. N.C., No clostridia grown. S, Sterile on culture.

Thirty original cultures were Gram-positive and 10 of these remained so after four weeks and 20 became Gram-negative. Twenty-one original cultures contained clostridia, of which 11 still had clostridia and 10 of them were free after four weeks. The continued presence of Gram-positive organisms and clostridia in some of the cases was probably due either to an insufficient dosage of penicillin or to an adequate dose being given but failing to reach all the Gram-positive organisms. Some Gram-positive organisms are not penicillin-sensitive. Towards the end of the investigation it was possible to have staphylococci tested for their sensitivity to penicillin, but in none of the cases could this be done for the original and four-week cultures. In addition it must not be forgotten that any residue of Gram-negative pus left in the wound after the penicillin course is completed would form an admirable medium for the proliferation of Gram-positive organisms still extant. It was noted that in wounds where pus was found at the first dressing it was mostly evil smelling and was later shown to contain Gram-positive organisms.

Thirteen original cultures which had no clostridia acquired them after four weeks, although the dressings had been sealed off during this period. The most probable explanation of this anomaly is that the swab of the wound taken at the beginning either failed to find clostridia that were present in the wound or the clostridia failed to grow from a swab that contained them.

Only 4 original cultures were sterile and this is too small a figure to be of any significance.

Relation of Penicillin Dosage to Change in Flora.—

Organisms		*Penicillin*
Original Culture	*Four-week Culture*	*Average Dose Per Patient*
G.P.	G.N.	802,600 units
G.P.	G.P.	621,200 ,,
G.N.	G.N.	765,000 ,,
G.N.	G.P.	910,310 ,,
C.	C.	632,000 ,,
C.	N.C.	835,000 ,,
N.C.	C.	753,000 ,,
S.	G.N.	570,000 ,,
S.	G.P.	570,000 ,,

The average dosage of penicillin given to patients from whom Gram-positive organisms were grown at the end of four weeks was 699,260 Oxford units, and to those from whom Gram-negative organisms and no clostridia were grown was 803,000 units. This difference in dosage suggests that some of the patients received inadequate quantities of the drug, and confirmation of this idea was gained clinically from the temperature charts of the patients treated at the beginning of the penicillin series when each man's course was strictly limited to five days. In the later cases the dosage of penicillin was regulated in accordance with the patient's clinical condition as shown by his temperature and pulse. On the whole a favourable change in the wound flora occurs with the larger average dosage of penicillin.

THE CONTRAST SERIES

These patients received their final form of traction and immobilization usually two or three days after their arrival at the Centre. Twenty-four hours were always allowed as routine for the patients to recuperate after their journey, during which period minor adjustments to the Tobruk plaster were made if necessary; the wounds were inspected only if the general condition of the patient or the remarks on the Field Medical Card suggested that delay was inadvisable. The first fifty patients were set up in three weeks during a rush of battle casualties in a ward understaffed, and during this period it was not possible to take all precautions to ensure adequate drainage of the wounds, and it is likely that had this not been so the number of cases in which loculation of pus occurred might have been lower. However, the dressings were not disturbed during the first three or four weeks and so, automatically, the conditions were similar to those imposed on the patients treated with penicillin as an experimental requirement. At the time of setting up of these fractures the wounds were not excised any further (as this had been done adequately by the Forward surgeons), but a general toilet was performed and the wounds were trimmed. Sulphanilamide powder and vaseline gauze formed the routine dressing. The large majority of the fractures were treated on mobile skeletal traction unless they were already sufficiently pulled out or unless there had been loss of bone. Splintage varied according to the fracture site and from the point of view of this investigation this variation is only of importance with regard to the fractures of the lower third of the femoral shaft, because it was in this type of fracture that 'sumping' of pus in the thigh occurred most frequently.

These fractures were treated on Thomas's splints bent at the knee with a plaster key sling to control the lower fragment, but in doing this the thigh was necessarily elevated to 45° or over and any loculation of pus tracked up the thigh

to form a gravitational abscess. It was this fact that led later to the use of postural drainage, both for the cases in which sumping had occurred and for those in which it was feared that it might occur.

THE PENICILLIN SERIES

It was considered that with twenty-four hours' preparation with penicillin given parenterally, it would be justifiable partially to suture the wounds of open fractures of the femur. Should this measure prove successful, it was argued, a wound would only have a small area to cover with granulations, the scar would probably be mobile, the time taken in healing would be diminished, and the open fracture would soon become closed. In addition, with the aid of penicillin it was thought that open reduction of the fragments and if necessary internal fixation would both be legitimate procedures.

The wounds of all the patients treated with penicillin, after the standard surgical toilet, were sutured in some degree varying with the size of the wound, the mechanical difficulty of approximating the wound edges, the degree of muscle loss, the presence of dead space, and consideration of drainage. None of the missile wounds were sutured completely, but fresh incisions such as were required for plating were stitched up entirely. The ideal aimed at was to suture each wound leaving only a small gap over the mouth of the original missile track, preferably at its most dependent point. In most of the cases no additional incision was made to provide extra drainage on the supposition that penicillin would control the infection. Later this supposition was thought not to be justified, and this policy must be held to be responsible for the number of cases that showed sumping, which, compared with the number in the contrast series, was excessive. Undoubtedly reliance on the power of penicillin led to the deliberate transgression of an elementary surgical canon, and later when these sumps had to be drained they contained considerable amounts of what proved to be Gram-positive pus. Except in those cases where fragments were reduced by open operation, with or without internal fixation, the methods of immobilization in this series were identical with those used for the control cases.

RESULTS

Deaths.—

Control Series	*Penicillin Series*
70	70
6 (8·5 per cent)	1 (1·4 per cent)

There have been 7 deaths, of which 6 were from the control and 1 was from the penicillin series. One of the deaths among the controls was due to profound toxæmia associated with sepsis in the affected thigh which had yielded neither to drainage nor to amputation. Of the remaining 5 cases, the causes of death were respectively: anaerobic toxæmia (*B. œdematiens*), which was too far advanced for amputation to be of help and which proved resistant to the use of anti-gas gangrene serum and to pencillin; gas gangrene following ligature of the external iliac artery in close proximity to an iliac colostomy for repeated secondary hæmorrhages; renal failure due to "transfusion kidney"; bronchopneumonia; septic infarcts of the lungs in a patient who died a few hours after admission before any treatment of the fractured femur could be carried out.

The one death in the penicillin series followed cerebral embolic lesions involving both striate nuclei and the left cerebral peduncle, which occurred during the operation at the Casualty Clearing Station; the patient on admission to the Centre was already suffering from athetosis. There is no mortality in the penicillin series that can be ascribed to sepsis.

The reduction of the mortality in the penicillin series is noteworthy. It would seem that patients in the contrast series succumbed to the concomitants of severe illness rather than to the sequelæ of an open fractured femur.

Amputations.—

Control Series	*Penicillin Series*
70	70
6 (8·5 per cent)	2 (2·8 per cent)

Eight above-knee amputations were performed; 6 on patients from the control series; and 2 from those treated with penicillin. Four of the six from the controls were done for gross sepsis with loculation of pus in the thigh and toxæmia that was endangering life and one of these patients eventually died in spite of amputation. Of the remaining 2 amputations, one was performed following ligature of the common femoral artery for secondary hæmorrhage; the other was for dry gangrene of the leg which had supervened as a result of injury to the popliteal artery and vein with consequent thrombosis.

Of the 2 amputations carried out on patients treated with penicillin, one was for gangrene of the leg which developed after ligature of the femoral artery in Hunter's canal, where it had been torn by a large loose fragment from the comminuted fracture of the femoral shaft at this level; the other was done as a procedure of election because the injury had damaged the leg beyond hope of reasonable functional recovery.

Secondary Hæmorrhage.—

Contrast Series	*Penicillin Series*
70	70
2 (2·8 per cent)	3 (4·3 per cent)

Two of the contrast series developed secondary hæmorrhage, one of which was controlled with a local pressure dressing and the other required ligature of the femoral artery and

amputation above the knee for consequent gangrene.

Secondary hæmorrhage occurred in 3 of the penicillin series, in one of which the femoral artery had been torn by a large loose fragment of bone at the site of the injury, but there was no evidence of sepsis in the wound at the time of hæmorrhage. One of the other two bled from the femoral artery in the lower end of Hunter's canal from a wound which contained multiple fragments of a grossly comminuted fracture and in which sepsis had not been fully controlled by penicillin; the other had three separate hæmorrhages of increasing severity before admission to the Centre which had been successfully controlled by a plug.

There is virtually no difference in the incidence of secondary hæmorrhage in the two series.

Progress at Four Weeks after Wounding.—A review of the fractures in both series was carried out and a comparison was made of the state of healing of the wounds in the penicillin series with that of the controls.

	Controls		*Penicillin*	
Total	61		68	
		Percentage		Percentage
Healed	3	5	4	6
Unhealed	58	95	64	94
Bone shut off	34	56	41	60
Bone not shut off	27	44	27	40
Sumping	5	8	10	15
Pyrexia	29	48	28	42
No pyrexia	32	52	40	58

More clearly to define the terms used in the table above it should be stated that by healing it is meant that the wound is completely epithelialized. By bone shut off it is meant that, although an ulcer may still be present or granulations still purulent, the fracture is completely covered over with soft tissue and that there is no sinus leading down to bone. This criterion is of the greatest importance in assessing the potentiality of chronic sepsis to become established. Sumping refers to tracking and loculation of pus in the dependent parts of the thigh and the adequate drainage or prevention of such sumps proved to be one of the major problems.

The number of wounds healed in each series is virtually equal. In view of the strictness of the criterion used this was largely to be expected because none of the wounds was completely sutured, and the mechanical difficulty of healing in many of them, on account of their wide extent, rendered satisfaction of this requirement, in such a short time, very unlikely. The bone was shut off in about an equal number of cases in the two series, and this is a disappointing result because the aim of partial suture was particularly to promote rapid conversion of an open into a closed fracture. The number of cases which showed sumping was twice as high in the penicillin series as in the contrasts, and this must be explained as the result of partial suture of the wounds, because this practice was the main difference in technique between the two series. The partial suture must have produced inadequate drainage and the retention of pus which was either not controlled by penicillin or, after the drug had been discontinued, again became Gram-positive and caused all the bad effects associated with pus loculation. There is very little difference in the number of patients still febrile at the end of four weeks, although in many cases in both series the degree of pyrexia was quite small.

It was noted during the first four weeks that the patients who were receiving penicillin appeared to be less toxic than the controls, they had less pain, and were less anxious and more cheerful, while, apart from those in whom sumping occurred, the temperature chart showed a less irregular progress. Over a hundred men suffering from open fractures of the femur were treated in one ward, those having penicillin being congregated at one end, and it seemed that the septic odour that prevailed was mitigated in this part of the ward.

Progress at Eight Weeks after Wounding.—A total of 58 control and 45 penicillin cases has been inspected eight weeks after wounding.

	Controls		*Penicillin*	
Total	58		45	
		Percentage		Percentage
Healed	6	10	7	16
Unhealed	52	90	38	84
Bone shut off	38	66	24	53
Bone not shut off	20	34	21	47
Sumping	5	9	8	18
Pyrexia	—	—	14	31

Although the percentage of cases healed seems to be rather low, it is not unexpected in view of the strict demands of the term healed. Some of the cases unhealed have only a few patches of granulation tissue unepithelialized.

The measure of the success of penicillin in the treatment of open fracture of the femur must be estimated on its ability to control infection sufficiently early to increase the speed of closure of the fractures. Eight weeks from the date of wounding is considered to be a reasonable elapse of time for such closure to be effected, and therefore the number of fractures still remaining open after penicillin treatment should be noticeably less than in the contrast series if the drug has been successfully used. Unfortunately the above table shows that the percentage of fractures in which the bone has become shut off after eight weeks is less in the penicillin than in the contrast series. As there are fewer cases treated with penicillin that have reached eight weeks after wounding, it may be that these percentages are virtually equal, but there is not the obvious improvement in the penicillin series that could legitimately be expected. Sumping in the penicillin series still occurs twice as frequently as in the contrast series because of the difficulty of proper drainage once a sump has become established.

Progress at Twelve Weeks after Wounding.—A total of 50 of the controls and 32 of the penicillin series has completed twelve weeks from the date of wounding.

	Controls		*Penicillin*	
Total	50		32	
		Percentage		Percentage
Healed	8	16	6	19
Unhealed	42	84	26	81
Bone shut off	39	78	19	59
Bone not shut off	11	22	13	41
Sumping	5	10	2	6

The percentage healed is roughly equal in both series and is still low for reasons stated previously. The chronic sepsis rate as measured by the number of patients still possessing a sinus, has fallen in the controls from 34 per cent at eight weeks to 22 per cent, and in the penicillin series from 47 per cent to 41 per cent. At first sight these figures suggest that the cases treated with penicillin have progressed less favourably than the controls. As fewer patients treated with penicillin have reached twelve weeks than have the controls, it is possible that the percentage of patients with sinuses is about equal in each series, but it evidently means that penicillin has produced no demonstrable improvement in the incidence of chronic sepsis that results from open fractures of the femur.

The contrast series shows the same number of sumps as at four weeks, but the number in the penicillin series has diminished from 10 at four weeks to 8 at eight weeks and to 2 at twelve weeks. The last-mentioned number may be higher when all the figures are complete, but it will most likely represent the same type of sumping as in the controls—namely, that following gross loss of bone and consequent larger dead space which fills in but slowly. The response of sumps, in the penicillin series, is apparently more rapid and this is, in all likelihood, due to the correction of those manufactured by partial suture of the wounds. It is doubtful whether penicillin has made any impression on sumps resulting from the effects of missile trauma alone. The cure of a sump must be continuous and successful drainage is purely a surgical problem.

Most of the chronically septic patients are not showing evidence of much toxæmia and their hæmoglobin is being maintained at about the level of 75 per cent. When required, periodical blood transfusions are given.

Plating.—Plating of fractured femurs in war surgery must necessarily have a limited application because the majority of these fractures are grossly comminuted. If there are more than three fragments it is unlikely that the plate can be fixed securely enough to hold the fragments reduced or to render the fracture stable. On estimating the fractures, in both series, considered to be fit for plating on this account alone, it was found that not more than one in five was eligible. Internal fixation was not used on any of the contrast cases, but on the assumption that with penicillin partial suture of the wounds was a legitimate procedure, a trial was made of plating the fracture at the time the wounds were being sutured. More often than not an additional incision was required through which to carry out the operation because the missile wounds were not well enough placed to be used as an operative approach. In 5 cases, however, the original wound was used and the plating was performed with the minimum of additional trauma. A fresh incision, when made, was stitched up completely after the operation and the partially sutured missile wounds were used for drainage. Fourteen of the penicillin series have been plated.

ANALYSIS OF CASES PLATED
(14 *cases*)

Deaths	0
Amputations	0
Secondary hæmorrhage	0

CASES THAT HAVE REACHED FOUR WEEKS
(14 *cases*)

Healed	2
Unhealed	12
Bone shut off	10
Bone not shut off	4
Sumping	1
Pyrexia	4
No pyrexia	10

CASES THAT HAVE REACHED EIGHT WEEKS
(14 *cases*)

Healed	4
Unhealed	10
Bone shut off	10
Bone not shut off	4
Sumping	2
Pyrexia	3
No pyrexia	11

CASES THAT HAVE REACHED TWELVE WEEKS
(7 *cases*)

Healed	4
Unhealed	3
Bone shut off	4
Bone not shut off	3
Sumping	0

Two plates have been removed, one four weeks after it was introduced and the other after eight weeks. The first patient had a fracture at the junction of the middle and upper third of the femoral shaft with small entrance and exit wounds passing through thick muscle covering and at the operation pus under tension was let out. After the operation a similar state of affairs arose and a sump with pus under tension developed. In spite of a large drainage tube introduced into the bottom of the sump, toxæmia did not subside very much, the plate became loose and finally broke away from the upper fragment. The plate was removed and skeletal traction applied; the patient rapidly recovered, but he still has a sinus present.

The second case did not develop a sump, but a grumbling infection continued with considerable toxæmia and a persistent sinus. After eight weeks, during which there was little improvement in either the general or local condition,

the plate became loose and was removed together with one two sequestra.

The wounds of three of the cases healed by first intention (except for the drainage holes left in the missile wounds which rapidly granulated over) and these patients have had an easy convalescence. One patient who remained afebrile, but showed superficial infection of the missile wounds (although the operation wound healed soundly), developed a collection of pus under the operation scar after eight weeks which opened up a portion of the wound and discharged, leaving a sinus down to the bone; as yet the plating is still intact.

Callus is forming more slowly in the plated cases, and knee function, even in the three who have had an uninterrupted recovery, is no better than in those treated by orthodox methods.

A successful plating operation has all the glamour of effective drama both for the patient and for the surgeon, but the majority of the cases so treated have derived little more than immediate satisfaction. The relatively small number of fractures which can be termed plateable, and the risk of running a checkered post-operative course, together make the use of internal fixation in fresh war wounds more than a doubtful policy. Even in the successful cases the benefits of an easy and rapid convalesence do not promise a better functional result, and the apparent rapid progress in the first three weeks after operation is too often paid for by retrogression between the fourth and eighth weeks.

In addition to the 14 cases mentioned, 2 fractured femurs have been plated whose positions had not been sufficiently controlled during orthodox treatment to avoid inevitable delay in union. As penicillin was available open reduction and plating was carried out in both instances, after the missile wounds had completely granulated. As a result of these operations the fractures have been accurately reduced and, so far, position has been maintained.

The average interval between wounding and plating was eight days and the operations were, therefore, carried out at a time that is held by some authorities to be unfavourable. This was unavoidable because the patients arrived at the centre too late for immediate plating, and the use of penicillin was restricted to patients whose wounds were not over fourteen days old.

Drainage.—In both series the formation of a sump in the thigh occurred, and the problem of drainage proved difficult, but in its solution the methods employed were found to be useful in preventing loculation of pus from developing in later cases. Initially, reliance was placed on the use of a large-bore rubber tube, through a relatively small incision at the most dependent point of the sump, but this method did not prove entirely satisfactory, either because the drainage so provided was inadequate or because after removal of the tube the sinus which was left still permitted pus to mass in its depths. This method was most effective with fractures of the upper third of the femoral shaft where the fracture was itself in a dependent position and the drain could be kept short.

In the earlier cases sumping occurred most frequently with fractures of the lower third of the femur which were all treated on a Thomas's splint, bent at the knee in order to control the lower fragment, but this position inevitably placed the fracture high up and the pus was enabled to track down the thigh. At first, drainage was attempted by introducing a large-bore rubber tube into the sump, but without success. This method gave place to the use of a large postero-lateral incision, but again this was not completely effective and the drainage wound either deteriorated into a small sinus or healed over and ceased to drain. At this time postural drainage was introduced and was found to be particularly applicable to fractures of the lower third of the femur because they were already being treated with fixed skin traction on a Thomas's splint, and the addition of plaster cuffs enveloping the leg and the splint, above and below the wound, enabled these patients to be turned over to the prone position with little risk of disturbing the reduction. Patients treated in the prone position experienced discomfort during the first forty-eight hours and so assumed the position only at intervals until they became accustomed to it. After this probationary period they were able to maintain the position continuously both for sleeping and eating and were turned back only for dressings. Under this régime obstinately high temperatures subsided, toxæmia was much abated, and wounds rapidly granulated. Any fracture of the lower third of the shaft of the femur with an anterior wound was regarded as likely to produce a sump and postural drainage was used as a prophylactic measure with success.

There still remained, however, the problem of the infected fracture of the mid-shaft of the femur with pus loculation. These fractures, as a routine (unless there was bone loss or fear of producing distraction), were treated with skeletal traction and mobile weights, and unless this was converted to fixed skin traction postural drainage could not be used. Whenever possible, it was considered desirable to maintain mobile traction and, in this event, continuous aspiration of the loculus by the siphon principle was employed. This proved effective so long as the siphon was operating. Drainage by this method tends to be capricious because it is difficult to prevent the eye of the drainage tube from impinging on soft granulations and so sealing itself. So long as this tube can be kept free the patient's temperature remains normal. The apparatus requires constant supervision and its temporary blocking is quickly followed by a rise of temperature.

It became apparent that only by the prevention of a sump from forming could the difficulties

of its treatment be circumvented. It was found that, although a wide-bore rubber tube failed effectively to drain a sump, yet, if it were used as a prophylactic measure at the first operation, the wound drained sufficiently well to avoid loculation of pus. As yet cases so treated have not developed a sump.

Chronic Infection.—Any patient whose fracture has not become shut off eight weeks after his injury is considered to have chronic infection. The percentage of patients in the contrast series who, according to the above definition, have chronic infection is 36 per cent and of the penicillin series is 47 per cent. In some instances the size of the wound may be responsible for the delay in healing, and in others inadequate drainage and possibly the presence of sequestra. A substantial reduction in the chronic sepsis rate is to be expected in a further four weeks, especially if satisfactory drainage is provided and sequestra removed. The percentage of the patients who have reached twelve weeks after their injuries and are still classified as chronically infected is 22 per cent in the contrast series and 41 per cent in the penicillin series.

In addition to giving attention to the local condition, care of the patients' general condition is of the greatest importance. Chronic toxæmia, anæmia, and persistent protein loss are the inevitable concomitants of chronic infection with the added danger of the development of renal calculi. Periodical estimations of hæmoglobin and of red cells were done and blood transfusions given.

As yet there has not been the means of determining the protein content of the blood and reliance has been placed on blood transfusion and the high protein diet that is customary in the Army for protein replacement.

All patients are taught to move about the bed as much as possible and have daily instruction from masseuses in movements both of the affected limb and the rest of the body. Physical training is instituted as soon as the patients will benefit by it. There has been no instance of urinary disability nor any evidence of renal calculi developing in any of the patients.

SUMMARY

Two main points emerge as a result of the present investigation. Penicillin, as used in this series of cases, failed to control sepsis fully and did not diminish the incidence of chronic infection. The second point follows from the first. Penicillin is not a substitute for surgery, and the greatest care and attention to surgical technique and to fundamental surgical principles are essential.

The power of penicillin to control infection is not held in doubt, but the method of its application to the problem of the open fractured femur in war surgery, with its concomitant laceration of soft tissue and comminution of bone at the bottom of a deep cavity, is the aim of the present inquiry. It is well known and has been repeatedly demonstrated that penicillin can master virulent and anaerobic infections in cavities such as the chest and knee where the disturbance is surrounded by a serous membrane. But the cavity surrounding the fractured femur is not so circumscribed, its efficient drainage is difficult, and pus is liable to track along the fascial planes. It was argued, for these reasons, that parenteral administration of penicillin would probably be more effective than local instillations which have proved so efficacious in the serous cavities. The wealth of local blood-supply suggested that the concentration of the drug at the fracture site would be both rapid and abundant. This being so, then the decision partially to close wounds and to use internal fixation for the bone would seem to be justified. The success of some of the plating operations and the healing of some of the wounds have been a measure of justification for the policy adopted, but the failure of these successes to be consistent, and the apparent increase of actual and potential sumping, argue that the drug is not powerful enough to overcome the consequences of surgery that is not strictly according to the rubric. It is felt that too enthusiastic an endeavour to convert a heavily infected, highly traumatized, open fracture of the femur into a closed one may easily lead to an unwise disregard of elementary surgical caution, or at least to the taking of risks that would not be taken were no penicillin used. It is noteworthy that in one or two cases whose post-operative course was uneventful and even afebrile the wounds broke down to form sinuses eight weeks after injury, and that although until this time the patients showed no evident toxæmia their condition then deteriorated and they rapidly acquired the characteristics of the patient suffering from chronic infection.

Two positive gains in the penicillin cases are clear, namely the reduction in mortality and in the number of amputations. To these must be added the clinical impression that the early weeks of convalescence were much easier than in those of the contrasts, and the toxæmia and anxiety were apparently less. The present series is obviously far too small finally to decide either the value of penicillin in fractures of the femur or the best methods of its application. Apart from the outstandingly good results (which are dramatic enough to overshadow the more sober evidence of comparative figures), the position is being reviewed in this interim report with the purpose of framing a policy for the future of the patients at present under treatment and of offering suggestion for the line of approach to the patients that will have to be treated.

The value of the inquiry lies in the assessment of the mistakes made and of the faults committed in the methods of employing penicillin,

rather than in an attempt to decide to what degree the drug is capable of controlling the career of a patient with an open fracture of the femur. It is certain that penicillin can never be more than a useful auxiliary, and it is worth reiterating that the problem of the infected fracture is still primarily one of surgery and not of bacteriology.

CONCLUSION

It is proposed that in the future, treatment of open fractures of the femur with penicillin should be modified in the light of the results obtained in the present series.

It is not considered desirable entirely to abandon the principle of partial suture of wounds; because successful suture is the method best calculated to increase the speed of closure of the fractures. It is thought essential, however, that when the wounds are sutured proper drainage must be instituted at the same time. Although the use of a drainage tube proved inadequate for emptying a sump, more recent experience has shown that a tube passed from a dependent part of the thigh up to the fracture site, at the time of wound suture, drains small amounts of fluid daily and that, by the time it is removed, the œdema of the thigh has subsided. Very often there is a missile wound appropriately placed to be used for drainage purposes, but if there is not it is advised that a counter incision be made.

Internal fixation is not regarded as a method of choice even in the small proportion of cases in which it is applicable because it is not considered that the benefits obtained by successful fixation are great enough to warrant the element of risk of serious infection with which it seems to be attended.

It is still proposed to rely on parenteral administration of penicillin, as it is thought that the fracture site is neither anatomically nor pathologically suitable for local instillations of the drug really to be of benefit. Although the average course of penicillin lasts about eight days, it is felt that the dose for each case should be decided according to clinical observations, especially the temperature, pulse, and the appraisal of the degree of toxæmia. Some patients appear to relapse after the presumably sufficient dose of penicillin has been given, and it has been suggested that such cases would benefit by a full course of sulphathiazole by mouth. It is possible that such relapses are due to a residue of bacteria that are not sensitive to penicillin and it is conceivable that sulphathiazole may be able to deliver the *coup de grâce*.

In view of the time lag between treatment in the Forward Area and definitive treatment at the Base, it is suggested that a method should be developed whereby penicillin can be given during this period. Parenteral injections may be too difficult a matter to be arranged. One patient arrived at the Centre into whose wound a cellophane sachet of penicillin had been introduced by a surgeon in the Forward Area in the hope that the penicillin concentration in the wound would be kept up by dialysis of the drug from the sachet, but a swab taken from the wound when the sachet was removed showed a plentiful growth of penicillin-sensitive *Staph. aureus*.

Finally, it must be repeated that the outstanding feature of the experience gained during the care of this group of fractures is the reaffirmation of that ancient surgical axiom that an infected wound requires drainage. Even penicillin cannot be expected to clean Augean stables.

BATTLE CASUALTY FRACTURES OF THE FEMUR: TREATMENT WITH PENICILLIN

By R. J. B. McEWAN, Major, R.A.M.C.
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This is a report on 12 battle casualties with compound fractures of the femur, treated by intramuscular injection of sodium penicillin at an orthopædic centre in Italy in 1944. Owing to the restricted supply of the drug, only the most severe cases were selected for this treatment.

TECHNIQUE OF TREATMENT

In each case treatment began within 15 days of wounding, and was conducted as described below.

1. Treatment of the Wound.—Invariably the wounds had been dealt with surgically in forward units by trimming, removal of dead tissue and foreign matter, and drainage. Firstly, a wound swab was taken for bacteriological examination. The surrounding skin was washed thoroughly with soap and water and reshaved, and the whole area, including the wound, was washed with saline. The wound or wounds were then 'revised' and, if necessary, completely excised. The skin edges were undercut and sutured together, often under considerable tension, with interrupted silkworm gut sutures, leaving an area about the size of a shilling unsutured to allow for the escape of discharges. No counter-incision was made for dependent drainage. In

some of our cases the wounds were so large that secondary suture was impossible. A dry dressing was applied and was not disturbed for 21 days. At the end of three weeks, the first dressing was done and the sutures were removed; further dressings were performed as infrequently as possible—namely, once a week or once per month. Wound swabs were taken at each successive dressing.

2. Treatment of the Fractured Femur.—This was the same as for any similar fractures treated without sodium penicillin. The Thomas splint was used for most, with either skin traction or skeletal traction; fractures in the hip region were treated chiefly in hip spicas. No retardation in the rate of union followed the exhibition of sodium penicillin.

3. Sodium Penicillin.—Each of the 12 cases received a 5-day course of intramuscular injections. The first injection was given in the theatre during the operation; thereafter injections were repeated every three hours for the first three days and four-hourly on the fourth and fifth days. Each injection consisted of 15,000 units in 2·5 c.c. of distilled water, and the total 5-day course amounted to 540,000 units. Most patients complained of local pain with the injections and they did not relish their frequency; but in no case was the complaint so serious that the intravenous route had to be substituted.

Most cases had received sulphanilamide or sulphathiazole orally in the forward units; this was continued in hospital until a maximum of 30 g. had been given unless operated upon before completion of the 30 g. Also, many cases had received anti-gas gangrene serum and anti-tetanic serum before arrival; but rarely was either a sulphonamide or anti-gas serum used after the commencement of penicillin treatment.

Early Effects.—The early post-operative effects of penicillin treatment were striking. There was immediate improvement in general condition, almost complete disappearance of toxæmia, and there was no local swelling of the fractured limb. The dressings gradually became stained with reddish discharge—" Gram-negative pus "—and usually had the characteristic odour of *B. proteus*. At the first dressing on the twenty-first day, there was complete lack of inflammation and of induration of the part; the granulations were clean and healthy. In most cases we noted that, although

RESULTS OF TREATMENT OF 12 CASES OF COMPOUND FRACTURE OF THE FEMUR WITH PENICILLIN

Case No.	Site of Fracture	Cause	Type of Wound	Infecting Organism	Nature of Operation Performed at Commencement of Penicillin Injection	No. of Days after Wounding when Operation Performed	No. of Days after Sodium Penicillin Course when Wound Healed	Union of Fracture	Result
1	Distal end, involving knee-joint	Shell wound	Perf. knee-joint	Staphylococcus, streptococcus	Trimming, Secondary suture	9	71	Yes	Complete success
2	Distal end involving knee-joint	Shell wound	Pen. knee-joint	Clostridia	Removal of foreign body. Trimming. Secondary suture	9	55	Yes	Complete success
3	Distal end, involving knee-joint	Shell wound	Perf. thigh	Staphylococcus, streptococcus	Trimming. Secondary suture	7	26	Yes	Complete success
4	Distal end involving knee-joint	Shell wound	Pen. knee-joint	Sterile	Trimming. Secondary suture	7	22	Yes	Complete success
5	Shaft	Machine-gun bullet	Pen. thigh	Staphylococcus	Secondary suture	14	44	Yes	Complete success
6	Shaft	Shell wound	Pen. thigh	Staphylococcus	Trimming. Secondary suture	8	18	Yes	Complete success
7	Shaft	Shell wound	Perf. thigh	Clostridia. *B. pyocyaneus*	Excision. Suture impossible	10	Unhealed, 100 days	Early union	Failure
8	Shaft	Machine-gun bullet	Perf. thigh	*B. proteus*	Trimming. Secondary suture impossible	14	Unhealed, 140 days	Yes	Failure
9	Subtrochanteric	B. W., grenade	Pen. thigh	*B. coli*	Trimmed. Not sutured	10	79	Yes	Complete success
10	Incomplete. (1) Femoral neck; (2) Both condyles	Shell wound	Three pen. wounds of bones	*B. proteus*	Excision. Secondary suture	9	34	—	Complete success
11	Femoral neck and great trochanter	B. W., aerial	Perf. buttock	*B. coli*	Trimming. Secondary suture	13	91	Yes	Complete success
12	Upper shaft and great trochanter	Shell wound	Pen. buttock	Wound swab not taken	Trimming. Secondary suture	4 4	Unhealed, 143 days	Yes	Failure

the wounds granulated rapidly, yet those granulations were slow to epithelialize—several weeks elapsing before they were finally covered with skin.

The table on previous page shows the results of treatment of the 12 cases :—

RESULTS

Successful Cases.—Treatment was completely successful in 9 of the 12 cases—i.e., the open fractures were converted into closed ones and bony union proceeded normally. After four years' experience of war wounds, we would not have had the courage to close them promptly without the aid of penicillin. Certain of these successes were truly remarkable :—

Case 11 had two buttock wounds, one of which measured 9 in. × 4 in. ; there was very extensive destruction of the buttock muscles and comminution of the great trochanter and femoral neck. The wounds were closed 13 days after injury. Healing occurred without complication.

Case 9 had large wounds of the lateral side of the hip, with comminution of the trochanters and femoral neck and multiple large retained metal fragments. It was not possible to close the wounds, but healing occurred despite the retained metal.

These compound fractures of the hip with gross muscle destruction are the type of case above all others demanding closure with penicillin. With other forms of treatment the usual sequel is prolonged suppuration and invalidism and even worse.

Case 2 had a penetrating wound of the right knee-joint with a large metal fragment embedded in the bone ; there was considerable comminution of the distal femur, gas bubbles were exuding from the wound, and clostridia were present in the wound swab. After removal of the metal, the wound was closed 9 days after wounding. Uncomplicated healing was complete in 55 days.

Unsuccessful Cases.—Three cases are described as failures because the fractures are still open ones three months after treatment ; but their progress has been far better with penicillin treatment than it would have been with any other, and there has been no anxiety for life or limb.

Case 7 had huge thigh wounds with gas gangrene and considerable muscle loss and a two-inch gap in the femoral shaft. It was impossible to close the wounds. Now, 100 days after his 5-day course of penicillin, healing is complete except for two small granulating sinuses leading down to bone, and the femoral gap has been bridged by a strut of new bone half an inch in diameter.

Case 12 has a small discharging sinus in the gluteal fold 143 days after his original treatment, and a low-grade bone infection is present.

In the light of experience gained, these cases might not have failed if a longer course of penicillin had been given.

Case 8 has a bone sinus 140 days after treatment. His wounds were so large as to prevent attempts at closure.

In none of the failed cases was the infecting organism tested for resistance to the sodium penicillin which was being used.

CASE REPORTS OF ILLUSTRATIVE CASES

Case 3.—**B.C. Multiple shell wounds (H.E.) : (1) Perforating left thigh with compound fracture of left femur, lower third involving knee-joint ; (2) Perforating right leg with compound fracture of tibia.**

Dec. 27, 1943.—Wounded. Admitted to Casualty Clearing Station 6 hours later.

OPERATION : (1) Perforating wound lower left thigh into knee-joint, shattering lower femur. Wounds excised, sulphanilamide and vaseline gauze. Tobruk plaster. (2) Perforating wound lower right leg excised. Sulphanilamide and vaseline gauze and plaster.

Dec. 31.—ADMITTED ORTHOPÆDIC CENTRE. General condition good. Temperature 100° F. Both lower limbs comfortable.

X-ray.—(1) Left femur : comminuted fracture of femur, lower 3rd, involving knee-joint, posterior angulation (*Fig.* 82). (2) Right tibia : comminuted fracture of lower tibia, ankle-joint not involved.

Jan. 3, 1944.—

OPERATION (7 days after wounding) : Plasters removed. (1) Left thigh : One large excised clean-looking wound on either side of lower 4th of thigh. Vaseline gauze drains removed. Skin edges excised and secondary suture of both wounds performed. Steinmann pin inserted through left tibial tubercle. Thomas splint skeletal traction. (2) Right leg : Very large clean wounds on either side of the leg above ankle. Impossible to close wounds owing to considerable skin loss. Dry dressing, plaster. First injection of sodium penicillin given in theatre.

Culture.—(1) Left thigh : *Staph. albus* and anaerobic streptococci. (2) Right leg : *Staph. albus.*

Jan. 8.—Five-day course of penicillin completed —total of 540,000 units. Temperature normal. No pain.

Jan. 29.—First dressing of left thigh. Both wounds have granulated level with skin, not epithelialized. This is now a closed fracture.

Culture.—No growth.

March 6.—Wounds of left thigh soundly healed (epithelialized). Steinmann pin removed. Clinical and radiological union of fractured femur in good position. Right leg : Plaster removed for the first time since application on Jan. 3. Wounds considerably smaller, clean and dry, but there has not been much attempt at healing. Several small sequestra and fine pieces of metal removed from bone. These wounds have a peculiar 'mummified' appearance. Early union. Replaster.

Culture.—Proteus.

March 12.—Jaundiced. Infective hepatitis.

April 9.—Evacuated. Wounds of left thigh still soundly healed, 30° active movement at knee-joint, gradually increasing (*Fig.* 83). Right leg in plaster, wounds still unhealed.

Comment.—Successful and early closure of the fractured femur, the wounds of which were sutured.

Case 7.—**B.C. shell wound (H.E.): (1) Through-and-through wound right thigh with compound fracture, femur; (2) Through-and-through wound, left thigh; (3) Through-and-through wound, left elbow.**

FIG. 82.—*Case* 3. Fractured femur soon after wounding.

FIG. 83.—*Case* 3. Three months later.

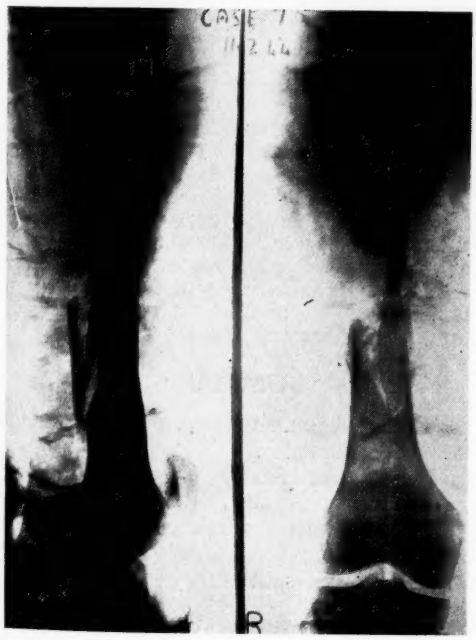

FIG. 84.—*Case* 7. Fractured femur soon after wounding.

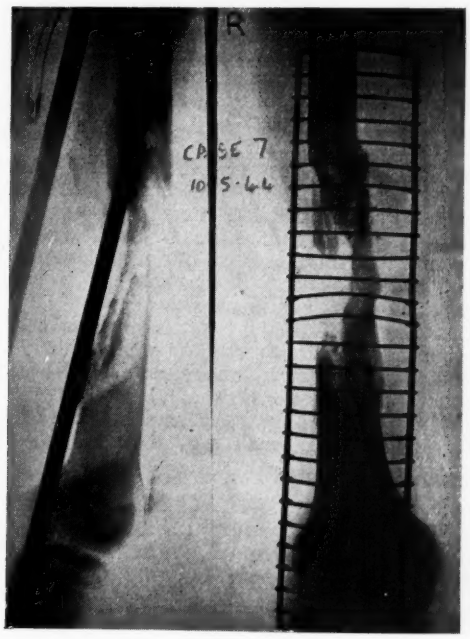

FIG. 85.—*Case* 7. Three months later. Persistent minor infection due to small sequestrum.

Feb. 2, 1944.—Wounded. Admitted Field Surgical Unit 8 hours later. General condition very poor. 2 pints plasma, 1 pint blood.

OPERATION: (1) Excision of extensive through-and-through wounds of right thigh. Shattering of bone. *Gas gangrene of muscle* with thin offensive discharge. Considerable local excision of vasti necessary. Vessels and nerves intact. Penicillin in wound. (2) Excision of through-and-through wound anterior left thigh. Complete division of quadriceps muscle, offensive and gangrenous. Much local excision including resection of 4 in. of sartorius. (3) Arm wound excised. Condition after operation very poor. Post-operative: 49,500 units anti-gas gangrene serum in theatre; 49,500 units 10 hours later; 24,000 units penicillin intramuscularly in theatre followed by 15,000 units 3-hourly; 49,500 units anti-gas gangrene serum daily intravenously.

Feb. 4.—No real improvement.

Feb. 5.—Some definite improvement. Penicillin and anti-gas gangrene serum stopped. Total penicillin: (*a*) Insufflation of wound; (*b*) 400,000 units intramuscularly. Total anti-gas gangrene serum, 198,000 units intravenously.

Feb. 11.—ADMITTED ORTHOPÆDIC CENTRE. General condition—fairly good, although looks pale and exhausted. One pint blood given.

X-ray.—Comminuted fracture of femur with gross destruction of bone—gap of 2 in. (*Fig.* 84).

Feb. 12.—OPERATION (10 days after wounding): (1) Right thigh—wounds lateral and medial of lower third of thigh, both 4 in. × 5 in., with considerable muscle loss—very clean—wounds connected with one another. Wounds trimmed, and although it was impossible to close the wounds completely, the skin edges were brought together over upper third of each wound. (2) Left thigh—wounds clean—closed completely with sutures. (3) Left elbow—closed.

Five-day course of penicillin, 540,000 units in all.

Culture.—Coliforms, *B. pyocyaneus*, clostridia.

Feb. 14.—Leg very comfortable. Temperature 99° F. General condition good.

Feb. 21.—Left thigh—sutures out of medial wound. Anterior wound half healed, slight discharge from centre of wound which had broken down—superficial. Left elbow—healed. Right thigh—dressings not touched—some discharge has come through but not sufficient to cause interference.

March 5.—Right thigh—sutures removed. Lateral wound—upper third healed. Anterior wound—upper 1 in. healed, other sutures burst out. Wound still connects with fracture.

Culture.—*B. pyocyaneus.*

March 24.—Left thigh—wounds healed. Right thigh—wounds have closed in rapidly, but the centre portion of each still extends down to bone.

April 3.—Right thigh. *Culture*: Proteus. Gram-positive cocci.

May 10.—*X-ray*: The gap in the bone has been bridged, and he now has a bridge of bone about ½ in. in diameter connecting the upper and lower fragments. Small sequestrum present. (*Fig.* 85.)

May 20.—Right thigh—wound is still discharging and connects with the bone but has shown a very marked improvement. There is very little bone infection. Patient is still on treatment.

Comment.—Although we have classified this case as a failure, because there is still a sinus present and some bone infection three months after wounding, the general progress has been most satisfactory. The patient has recovered from gas gangrene and is getting bony union in a fractured femur in which there was a considerable bone gap.

Case 11.—**B.C. B.W. (Aerial) perforating right hip with compound fracture of great trochanter and neck of right femur; with partial sciatic palsy.**

Jan. 22, 1944.—Wounded. Admitted to Field Surgical Unit.

OPERATION (3 hours after wounding): Large wound of right buttock and thigh, smaller wound upper right buttock, edges of entry trimmed, fascia split crucially. Exit wound trimmed and enlarged in length of limb to expose gross muscle damage. Damaged muscle excised. Fracture of great trochanter and neck of femur, 2 loose fragments removed. Cramer wire splint. Anti-gas gangrene serum, 49,500 units intravenously. One pint plasma.

Jan. 24.—Tobruk plaster. One pint blood.

Feb. 1.—ADMITTED ORTHOPÆDIC CENTRE. General condition fair. Temperature 100° F. Pain in right hip. Has completed 25 g. of sulphanilamide by mouth.

X-ray.—Right hip: Comminuted fracture of great trochanter and base of femoral neck, good position.

Feb. 4.—OPERATION (13 days after wounding): Tobruk plaster removed. Two wounds present: (1) 1 in. × 1 in., above great trochanter. Fairly clean. (2) 9 in. × 4 in., in lower right buttock and upper thigh, dirty. Necrotic muscle excised and dirty granulations curetted away. Sciatic nerve (apparently intact) visible in the depths of the wound. The two wounds communicated through a tunnel deep in the buttocks. Secondary suture of both wounds performed under considerable tension without trimming as too much skin has been lost. Dry dressing. First injection of sodium penicillin given intramuscularly in theatre. Hamilton Russell traction in the ward.

Culture.—Coliforms; and Gram-positive bacilli and cocci.

Feb. 9.—Five-day course of sodium penicillin completed—total of 540,000 units. General condition good. Afebrile since operation.

Feb. 26.—First dressing. Upper wound healed. Larger lower wound healed except for central 2 in. which has granulated and is superficial. Clinically this is now a closed fracture. Hip spica applied.

May 5.—Hip spica bivalved. Wounds completely healed. Fractured femoral neck clinically and radiologically united. No recovery in partial sciatic palsy. General condition good.

Comment.—Successful and early closure of the fracture in a particularly dangerous area.

SUMMARY

1. Twelve open fractures of the femur were treated with penicillin.

2. Nine were firmly closed three months after wounding.

3. Three showed persistent minor infection at three months.

4. All showed satisfactory bone union.

GAS GANGRENE IN ITALY

A STUDY OF 33 CASES TREATED WITH PENICILLIN

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The progress of the British Army from the Middle East to Tunisia, to Sicily, and to Italy has been attended by a gradual increase in the incidence of gas gangrene among the wounded. This increase has been barely perceptible to the clinical surgeon, but is borne out by the figures of incidence—3·4 per 1000 in the Middle East, and 6·7 per 1000 in Tunisia (MacLennan, 1944). In Italy the true figure cannot yet be stated, but it will not be less than 10 per 1000. Although gas gangrene is now more common, as was to be expected when the cultivated fields of Europe became the battlefield, it is by no means rampant, owing to early and good surgery.

In Tunisia the mortality from gas gangrene was tending to diminish (30 per cent in 44 cases —MacLennan, 1944), and this improvement was rightly attributed to education of the surgeons in accurate diagnosis, full surgery, intensive serotherapy, resuscitation, and sulphonamide chemotherapy. In Sicily and Italy the mortality figures have been higher; 126 cases of gas gangrene were reported to the Army authorities from August, 1943, to February, 1944, with 62 per cent mortality (MacLennan and Macfarlane, 1944). By February, 1944, when the present investigation with penicillin was started, the surgeons were becoming increasingly experienced and the mortality was about 50 per cent. Similar statistics were noted by a group of American surgeons studying anaerobic myositis among American troops in Italy (Colonel E. D. Churchill, Consultant Surgeon—personal communication): in over 100 cases of undoubted gas gangrene the mortality was 54 per cent.

SELECTION OF CASES

This is a report of 33 cases of gas gangrene occurring in Italy in the spring of 1944, in which penicillin was given in an attempt to reduce the mortality. We accepted MacLennan's definition of gas gangrene as a clostridial infection of muscle, and included in this investigation only cases of undoubted true clostridial myositis. Indeed, so anxious were we not to claim merit for penicillin in doubtful cases, that we accepted well-established instances only for consideration in this report. Thus there were several cases of 'early gas gangrene', and cases of anaerobic cellulitis, successfully treated with surgery, antiserum, and penicillin, which we have not included. Apart from this method of selection, the cases formed a consecutive series of thirty-three. At the end of the main body of this report we have described an additional case under the term 'gas œdema'.

TREATMENT AND RESULTS

The 33 cases in this series were operated on by many different surgeons, but the basis of treatment which we recommended was the same, viz.: (1) Radical surgery, allied to full resuscitative measures with blood, plasma, and saline transfusions; (2) Gas-gangrene antiserum; (3) Penicillin.

1. RADICAL SURGERY

This remains the keystone of treatment, and no matter how much antiserum or penicillin is given the outlook is gloomy indeed if radical extirpation is not possible. In assessing the results we have classified under 'full treatment' all those cases in which at least a start was made with radical surgery, antiserum, and penicillin. All of the surviving cases were followed up until the patients were well on the way to good health, and never for less than one month after the disease abated:—

Total cases 33 Total deaths 12 (36·4 per cent)

In 5 cases surgery was either not possible at all owing to the patient's poor condition or amounted to incision alone into widespread disease, and though they began treatment with antiserum and penicillin, all died. It would be fallacious of course to attribute such deaths to lack of surgery *per se*; the deaths were due to the advanced nature of the disease.

Total full treatment 28 Total deaths 7 (25 per cent)

In these 28 cases an attempt was made fully to extirpate the disease (by amputation or excision), but it was noted at the time in 18 cases that the limit of disease process was not reached; either portions of gangrenous muscle were left in situ or there was œdema and gas in the intramuscular planes at the level of operation or in the abdominal wall. This suggests that if surgery can eradicate the greater part of the disease, antiserum and penicillin can check spread from gangrenous portions left behind. We have no evidence to produce of localized gas gangrene treated successfully without any surgery at all.

There was no significant difference between the survival rates following amputation and following excision. With penicillin to check clostridial growth, it had been hoped that localized excision of muscle might be possible more often than the more radical procedure of amputation. In the event it was found that of the 28 cases in which surgery was attempted, 20 had amputation performed. Thus amputation was in 18 cases properly indicated because the limb was going to

be a useless one anyway, owing to major vascular injury, severe fracture, or loss of more than one muscle group. In only 2 of the 20 amputations might it have been justifiable to do a more conservative operation. Localized excision, therefore, is only indicated where a single muscle group is affected, e.g., the adductor group of the thigh, or anterior tibial group. The corollary is that amputation is not performed simply because of gas gangrene, but to remove a useless limb.

Blood Transfusion.—Fullest use must be made of transfusion therapy, for apart from other considerations the clostridium produces a powerful hæmolytic toxin. Most of these 30 cases received about 4 pints of blood fairly quickly after operation, followed by plasma or saline as further supportive measures. Several days later the Hb reading in one or two cases was as low as 26 per cent, and further blood was required.

2. GAS-GANGRENE ANTISERUM

As a standard we recommended that the patient should have A.G.G.S., 49,500 units intravenously, immediately on diagnosis; to be followed in 6–8 hours by a further 49,500 units if there was no clinical improvement, and repeated again when necessary (Polyvalent gas-gangrene antitoxin, B. W. & Co. Three bottles, each of 9000 units *Cl. welchii*, 4500 units *Cl. septicum*, 3000 units *Cl. œdematiens* in 7·5 c.c.). It is desirable to have the antiserum circulating in the blood prior to operation because the trauma of operation may liberate toxin, but in practice it was usually given on the operating table after operation. While we feel certain that the antiserum given in these 33 cases must have contributed materially to the survival rate, we have no positive evidence to support it. Our conviction rests on previously published clinical and experimental reports. The average amount of antiserum given to the 21 cases that survived was 116,000 units; the 12 fatal cases received an average of 110,000 units.

While *therapeutic* antiserum is invaluable, we have yet to measure the value of *prophylactic* antiserum to prevent gas gangrene. In 10 of these 33 cases of gas gangrene the disease was already established when they came to first operation, and they are excluded from this particular discussion. Of the other 23 cases it is significant that no less than 10 had been given large doses of ' prophylactic ' antiserum, ranging from 16,500 units to 49,500 units at a previous operation. This was at a time when there was no evidence of gas gangrene and at least twenty-four hours before the diagnosis was made. In fact, the prophylactic antiserum did not prevent onset of the disease (*see Table III*). As to whether it increased the length of incubation period or lessened the severity of the disease, there is this evidence: The average incubation period of the 10 cases that were given prophylactic antiserum was 71 hours. The average incubation period of the other 13 cases, also inspected before disease was apparent, but not given antiserum, was 58 hours. The difference of 13 hours is slight. The severity of the disease, judging by the mortality rate, did not appear to be minimized:

	Cases	*Incubation Period*	*Deaths*
Prophylactic antiserum	10	71 hours	4
No prophylactic antiserum	13	58 hours	3

We have considered the question whether the giving of *prophylactic* antiserum might not have disadvantages sometimes under war conditions, since it cannot kill off the clostridia, and can only neutralize circulating toxin whereby symptoms may be masked and operation delayed. On the other hand, if it can neutralize the toxin in the barrier area it may give the clostridia a less favourable medium for development and thus slow the march of the pathological process. Weighing advantages against disadvantages, we feel that gas-gangrene antiserum can do more good than harm.

3. PENICILLIN

This is obviously the chemotherapeutic agent of choice meantime, since it can be shown *in vitro* to inhibit the clostridia of gas gangrene; it does so more surely than do the sulphonamides. A dose of 15,000 units intramuscularly at 3-hourly intervals provides the requisite blood concentration for inhibition.

In this series we advised an initial dose of 22,500 units sodium penicillin followed by a 3–5-day course of 15,000 units intramuscularly 3-hourly (120,000 units a day). As with the antiserum, the penicillin was usually first given on the operation table, but for preference should be given as early as possible. In a few cases the drug was given by continuous intravenous drip of blood, plasma, or saline, 5000 units per hour. This is satisfactory so long as the intravenous therapy does not have to be varied in rate, and there is certainty that the requisite amount of penicillin is being administered. The average dose of the 21 patients who survived was 370,000 units. Of the 12 fatal cases, 6 did not survive more than twenty-four hours, and received less than 120,000 units. The other 6 fatal cases received adequate doses, so far as arrest of the progressive myositis was concerned (300,000 units to 1,500,000 units).

370,000 units is not a large dose for a systemic course of penicillin, but it was felt that by the third day the patient would either have succumbed in a fulminating illness or would have mastered the infection. In the light of experience we would say that a 3-day course of penicillin is sufficient if there is a fair certainty that all the diseased muscle has been removed by surgery; but that if any gangrenous portion is left behind then the course should be a 5–10-day one. Furthermore, we believe that a re-assessment of the wound is desirable between the fifth and tenth days, with the patient now in better general condition, and gangrenous tags removed surgically

rather than being allowed to slough off. We felt that some of our late deaths were due to the toxicity of these retained products.

Of the value of penicillin in checking the spread of the disease we had no doubt. This was most clearly shown in these fatal cases in which it was known that gangrenous portions had been left in situ. They died later of causes such as bronchopneumonia and renal failure, and all showed arrest of the gangrene close to the original site. The more straightforward case, e.g., where amputation had been performed well above the gangrenous muscle, made a very rapid recovery, and in a few days the stump was clean enough to be sutured. This was so even though there was œdema and gas in the intermuscular planes at the level of amputation.

It was interesting to observe the length of time required for penicillin to get on top of a severe infection. The drug is bacteriostatic and appeared to need 36 hours to exert its effect. During this 36 hours the patient sinks downhill and there may even be increase in extent of the subcutaneous œdema and crepitus. Then suddenly, in the course of an hour or two, the moribund patient—sweating, unconscious, and with a subnormal temperature—becomes rational and may smoke a cigarette. It is, therefore, of paramount importance not to give up hope for patients who have had a fair start with surgery, antiserum, and penicillin, but to try by all resuscitative means to keep them alive during this critical period—blood transfusion, oxygen, brandy, coramine, and the whole armamentarium.

CASE-HISTORIES

The case-histories are summarized in *Table I*, and two typical examples are described in full.

Case 1.—**Gas Gangrene of Thigh—Fatal.** Pte. R., aged 21.

Jan. 22.—Shell wound of left thigh. Extensive soft-tissue wound of left thigh on medial aspect, with gross skin and muscle destruction. Bone, femoral vessels, and nerves intact.

Operation: Field Surgical Unit (6 hours after wounding). Pentothal. Excision of devitalized skin, subcutaneous tissue, and muscle. Wound left saucer-shaped, 6 in. × 4 in. Cavity lined with sulphanilamide and vaseline gauze. Plaster cast applied.

A.G.G.S. 22,500 units intravenously. Oral sulphonamide course.

Jan. 23.—Admitted to General Hospital. General condition excellent. Leg comfortable in plaster—not disturbed.

Jan. 29.—Complaining of frontal headache. Temperature 101°. Pulse 104. Dressings removed and wound inspected—appeared clean and healthy. Re-dressed with sulphanilamide and vaseline gauze.

Jan. 30.—Sudden deterioration of general condition. Temperature 101°. Pulse 150. Patient very ill, grey pallor, rapid feeble pulse. Rational, and complaining of pain in leg. On examination there was swelling of the thigh in the medial aspect, with crepitation over it and in the abdominal wall in left iliac fossa and loin. Pallor of skin of thigh.

Operation: Excision of adductor group of muscles, which were reddish-grey in colour, non-contractile and not bleeding, and obviously gangrenous. Gracilis, adductor brevis, longus, and most of magnus excised. Small tags of gangrenous muscle were left. Quadriceps group of muscles appeared healthy. There was a little gas in the tissues, and the smell was moderately offensive.

A.G.G.S., 49,500 units intravenously; penicillin, 22,500 units intramuscularly. Thereafter 15,000 units 3-hourly intramuscularly or in blood-drip. Blood, 2 pints during operation.

Eight hours later: Condition fair. Further A.G.G.S., 49,500 units intravenously. Penicillin continuing in blood-drip.

Jan. 31.—Condition worse, and very critical. Temperature 97°, pulse 130. Irrational. Crepitus up to costal margin, and swelling and discoloration above inguinal ligament.

Operation: Wound further opened up, with incisions through fascia into quadriceps—not affected. Excision of sartorius muscle, which was found gangrenous—probably oversight from first operation.

A.G.G.S., 49,500 units intravenously. Penicillin continuing.

Eight hours later: Moribund. Subnormal temperature. Imperceptible pulse. Clammy. Sighing. Unconscious.

Feb. 1.—Marked improvement in general condition. Conscious and cheerful. Later took food and read paper.

Feb. 3.—Improvement maintained. Much discharge through dressings—has been on continuous blood and glucose saline drip for 4 days. Crepitus still palpable up to costal margin. Swelling above inguinal ligament I.S.Q., but no increase.

Feb. 4.—Improving, though a bit restless. Crepitus palpable but diminishing. Still on penicillin.

Feb. 5.—Secondary hæmorrhage; died at 03·00 hours before he could be taken to operating theatre. Was given 1 pint of blood before death. *Note*: This hæmorrhage probably began earlier and was not noticed. He had been shifted to a new ward, no longer had a special nurse, and the lights had all failed in a storm.

POST-MORTEM EXAMINATION.—Bleeding had apparently come from one of the branches perforating the adductor magnus. Necrotic tags of adductor muscles in situ. No gangrene in rest of thigh or abdomen. Œdema and some gas in superficial tissues of abdominal wall. No gas in thigh.

SUMMARY OF TREATMENT.—

1. Surgery, localized excision of muscle.
2. Gas-gangrene antiserum, 148,500 units.
3. Penicillin, 602, 500 units.
4. Blood, 4 pints. Glucose saline, 13 pints.

Comment.—Onset of gas gangrene after 7 days. This was a tragic termination to a case that was recovering, and in which the gas gangrene had apparently been mastered. It seemed that about 36 hours were required before the bacteriostatic effect of penicillin became obvious, during which time there was slight increase in local disease, and the patient's condition became progressively worse. (*See Fig.* 86—temperature and pulse chart.)

Case 13.—**Gas Gangrene of Thigh—Recovered.** Pte. T., aged 23.

Feb. 7 (02·00 hrs.).—Shell wound of right thigh. Three pints of plasma given at the Regimental Aid Post. Admitted 4 hours later to Field Ambulance in state of shock (blood-pressure 90/60) and bleeding from large wound of thigh. Transfused before operation.

Table I.—DETAILS OF CASES

CASE	LESION	FRACTURE	MAJOR ARTERY DAMAGED	MUSCLE GROUPS INVOLVED	OPERATION	A.G.G.S. UNITS	PENICILLIN UNITS	RESULT	COMMENT
1	S.W., thigh	—	—	Adductors, *abd. wall*	Excision	148,500	602,500	Died	Full treatment
2	S.W., abdomen, thigh. Amputation	Femur	Ext. iliac	Thigh stump, *abd. wall*	—	49,500	97,500	Died	Incomplete
3	M.W., forearm	Radius, ulna	—	All forearm	Amputation	99,000	240,000	Recovered	Full treatment
4	S.W., leg	—	Popliteal	Ant. tibial, peroneal	Amputation	49,500	250,000	Recovered	Full reatment
5	S.W., leg	Tibia, fibula	Post. tibial	All leg muscles, *abd. wall*	Amputation	120,000	120,000	Recovered	Full treatment
6	S.W., back	—	—	Sacrospinalis	Excision	49,500	257,000	Recovered	Full treatment
7	M.W., leg	Tibia, fibula	Ant. and post. tibial	All leg muscles	Amputation	82,500	240,000	Recovered	Full treatment
8	S.W., thighs	R. femur	—	Quadriceps of both thighs	Excision	198,000	400,000	Recovered	Full treatment
9	B.W., thigh	—	—	Quadriceps	—	49,500	29,000	Died	Incomplete
10	Bullet, thigh	—	—	Rectus femoris, gluteals, *abd. wall*	Excision	165,000	345,000	Died	Full treatment
11	S.W., legs	Tibia, fibula (bilateral)	R. ant. tibial	Deep leg and calf muscles, R.	Excision	33,000	1,597,000	Recovered	Full treatment
12	S.W.,thoraco-abdominal	—	—	Buttock and thigh, from retroperitoneum	Incision	113,000	398,000	Died	Incomplete
13	S.W., leg	Femur	—	Lateral quadriceps, hamstrings	Amputation	83,000	413,000	Recovered	Full treatment
14	Bullet, leg	Tibia, fibula	—	All calf muscles	Amputation	99,000	390,000	Recovered	Full treatment
15	Bullet, thigh	—	Femoral	Quadriceps adductors	Amputation	49,500	397,000	Recovered	Full treatment
16	B.W., arm	Humerus (traumatic amputation)	Brachial	All upper arm	Disarticulation at shoulder	112,500	352,000	Recovered	Full treatment
17	S.W., buttock	—	—	All gluteal, pyriformis	Excision	336,000	395,000	Recovered	Full treatment
18	S.W., thigh	—	Femoral	Quadriceps	Incision	33,000	22,500	Died	Incomplete
19	S.W., thigh	—	—	Hamstrings, adductors	Amputation	150,000	360,000	Recovered	Full treatment
20	S.W., thigh	—	Femoral	All thigh muscles	Amputation	150,000	337,000	Died	Full treatment
21	M.W., legs	Tibia, fibula (bilateral)	L. ant. tibial	Left anterior tibial	Amputation (bilateral)	115,000	105,000	Died	Full treatment
22	S.W., thigh	Femur	—	Buttock, all thigh muscles	—	100,000	120,000	Died	Incomplete
23	M.W., leg	—	—	Calf muscles	Amputation	90,000	300,000	Recovered	Full treatment
24	S.W., thigh	Femur	—	Adductors	Amputation	100,000	427,000	Recovered	Full treatment
25	S.W., arm	Humerus	Axillary	Upper arm, shoulder girdle	Disarticulation—humerus and scapula	100,000	300,000	Died	Full treatment
26	S.W., arm	Humerus	Brachial	Biceps, coracobrachialis	Amputation	132,000	240,000	Recovered	Full treatment
27	S.W., thigh	—	—	Adductors, medial hamstrings	Excision	99,000	405,000	Recovered	Full treatment
28	S.W., leg	Tibia, fibula (traumatic amputation)	—	Adductors, *abd. wall*	Higher amputation	198,000	200,000	Recovered	Full treatment
29	S.W., thigh	—	—	Quadriceps	Excision	66,000	30,000	Died	Full treatment
30	M.W., leg	Tibia, fibula (traumatic amputation)	—	Adductors, *abd. wall*	Higher amputation	165,000	1,540,000	Died	Full treatment
31	S.W., forearm	Radius	Radial	All flexors of forearm	Amputation	66,000	120,000	Recovered	Full treatment
32	S.W., calf	—	Ant. and post. tibial	Anterior tibial, peroneal, soleus	Amputation	148,000	360,000	Recovered	Full treatment
33	S.W., thigh	Femur	—	Adductors, hamstrings, *abd. wall*	Disarticulation at hip	180,000	384,000	Recovered	Full treatment

S.W., Shell wound; M.W., Mine wound; B.W., Bomb wound.

Operation: Field Surgical Unit (6 hours after wounding). There was a through-and-through wound of the thigh, with an enormous exit wound, 11 in. × 8 in., involving the whole of the anterior aspect of the thigh with much tissue destruction. There was a considerable gap in the mid-shaft of the femur, and the exposed muscles were covered with a layer of manure. There were also soft-tissue wounds of the arm.

The wounds were excised and dressed with sulphanilamide and vaseline gauze. Thomas splint and fixed skin extension, with plaster (modified Tobruk plaster).

A.G.G.S., 33,000 units intravenously. Blood, 6 pints (before, during, and 24 hours after operation).

Feb. 8.—Although the patient looked well the temperature rose in the course of the morning to 102·6° F., and A.G.G.S., 33,000 units, were given intravenously. In the afternoon the patient looked ill. His colour was poor, he was somewhat confused, and he complained of pain in the limb. The wound was examined, and swelling and crepitus found in the thigh, especially on lateral aspect. Offensive smell.

Operation: Gas gangrene found in the lateral and posterior muscle groups, which were greenish-grey and non-contractile, with a few gas bubbles.

The leg was amputated through the fracture site. Gangrenous muscle was excised as far as possible, but some necrotic and œdematous tissue was left.

A.G.G.S., 50,000 units intravenously (total for the day, 83,000 units). Penicillin, 22,500 units intramuscularly; thereafter, 15,000 units 3-hourly (total for day, 52,500 units). Blood, 2 pints.

Feb. 9.—General condition improved. Temperature 101°. Pulse 120. Comfortable and slept well. No spread of gangrene detected, but the dressings had a strong smell.

Penicillin, 120,000 units intramuscularly. Blood, 1 pint. Plasma, 2 pints.

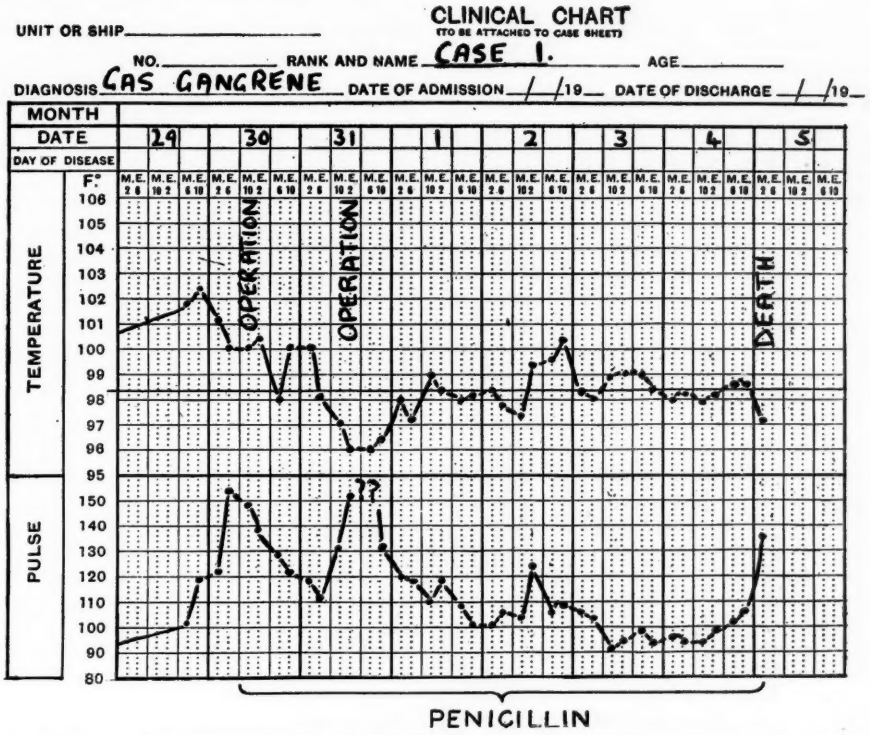

FIG. 86.—*Case* 1. Temperature and pulse chart, indicating moribund condition at 36 hours; followed by satisfactory course until death from secondary hæmorrhage. Improvement after 36 hours probably due to bacteriostatic effect of penicillin, and not to the second operation.

Feb. 10.—General improvement continued, and patient felt well. Temperature 99°. Pulse 108. Penicillin, 120,000 units intramuscularly.

Feb. 11.—The wounds were redressed and a few bubbles of gas came from between the flaps. The muscles were covered with a thin layer of greenish slough superficially, with a little pus formation. Underneath this, however, the muscles were healthy. Penicillin, 120,000 units intramuscularly.

Feb. 12.—Patient looked extremely well, and was evacuated to the Base.

Feb. 18.—Admitted to General Hospital. Condition good. Temperature 99°. Pulse 86.

Operation: Stump dressed. Skin edges gangrenous in parts. Superficial necrosis of muscle. Much foul pus present. Wound excised and partially sutured, with tubes for local penicillin instillations. Culture, *Cl. welchii*, *Staph. aureus*.

Feb. 27.—Stump now satisfactory. Had 26,000 units penicillin by twice-daily instillations for 4 days (250 units per c.c.). Culture, *B. pyocyaneus*.

April 4.—Stump well healed. Evacuated to U.K.

SUMMARY OF TREATMENT.—

1. Surgery, amputation.
2. Gas-gangrene antiserum, 83,000 units.
3. Penicillin, 413,000 units.
4. Blood, 3 pints. Plasma, 1 pint.

Comment.—Onset of gas gangrene after 30 hours, in spite of having been given A.G.G.S., 33,000 units, prophylactically 6 hours after wounding. Successful result from full treatment.

CLINICAL AND PATHOLOGICAL FEATURES

In 10 of the 33 cases the disease was already established when the patient came under observation, but in the other 23 it was possible to observe early clinical features. Toxicity, pain, and swelling were present in all of them, though sometimes the pain was obscured by the man's delirium. While swelling and pain are the earliest clinical features, it was noteworthy that it was usually the fairly sudden deterioration in the man's general condition that first drew the attention of the busy medical and nursing staff to the state of affairs. Other features such as smell, crepitus, gas, and pallor or discoloration of the skin were present to a varying degree in half the cases, showing that the disease was already well advanced—a fact which was confirmed by the more common finding of muscle that was grey or purple and pultaceous, rather than the earlier stage of light red non-contractility which was only occasionally noticed.

FIG. 87.—*Case* 30. Showing gangrene in the remaining adductors, five days after amputation for gas gangrene. The adductors were gangrenous at operation but not excised. Swelling and discoloration in the lower abdominal wall and hip, barely visible because of the patient's dark skin (Indian). The gangrene was arrested, but death occurred later from renal failure.

In 7 cases the disease had spread from the thigh to the abdominal wall, as evidenced by swelling, œdema, discoloration, and crepitus above the inguinal ligament. Three cases recovered (and we had never previously seen such a case recover). At post-mortem examination of the other 4 cases gangrene of the external oblique muscle was found in 1 case, but in the other 3 cases there was only subcutaneous œdema and gas. This finding suggests that 'spread to the abdominal wall' does not necessarily mean involvement of abdominal muscle. In any case it is recognized that subcutaneous spread can appear well in advance of the disease, and therefore spread above the inguinal ligament should no longer be regarded as indicating a hopeless prognosis. (*Fig.* 87.)

Site.—As will be seen from *Table II*, the thigh is the commonest site; and it is the most lethal because of the size of the muscle bellies involved, and the difficulty of getting above the limit of disease. It is also an area of free lymphatic drainage, and one fears disease in the adductor group and medial quadriceps most of all. Gas gangrene in the buttock, occurring not as a spread from the thigh but arising in a buttock wound, is not as serious as it at first appears. We have noticed this in 3 previous cases in the Middle East, all of which recovered without serious spread, although in 2 cases surgery was limited to incision. Gas gangrene of the leg and forearm should seldom be fatal, because with prompt surgery it is not difficult to get well above the limit of disease. The death of 1 case of gas gangrene of the leg was partly due to surgical shock, for the other leg also was shattered and required amputation, and the patient died within 24 hours.

Table II.—SITE INCIDENCE

		Back	*Buttock*	*Thigh*	*Leg*	*Arm*	*Forearm*
Total	33	1	1	18	8	3	2
Deaths	12	—	—	10	1	1	—

Fractures and Arterial Injuries.—Of the 33 cases, 14 had a major artery damaged, and 18 had an accompanying major fracture; 9 had both. Altogether 24 had either arterial damage or fracture; most of them required amputation. Only 3 of the 24 were treated by local excision —1 femur, 1 tibia, and 1 anterior tibial artery. While these lesions probably affected the incidence of the disease, their presence in itself was no guide to prognosis. In 9 cases there was no associated lesion, and 5 died. Only 1 of the 33 cases had had prolonged application of a tourniquet.

Time of Onset.—*Table III* shows: (1) The interval between wounding and first operation; (2) The time of onset of gas gangrene, or rather its clinical recognition; (3) The time of death in the fatal cases, reckoned as from time of wounding; (4) Whether prophylactic gas-gangrene antiserum was given at first operation.

The onset of gas gangrene in these 33 cases varied between 8 hours (possibly less) and 7 days, with 48 hours as the commonest time (*Table III*). This variation occurred even though the infecting organism was constant, for we found that *Cl. welchii* was by far the commonest pathogenic clostridium in Italy. *Table III* indicates that there was no significant difference in the prognosis between (*a*) gas gangrene discovered early, usually at first operation; and (*b*) gas gangrene developed later. Also, the cases of gas gangrene in which there was delay of over 24 hours between wounding and first operation were no more and no less serious than others. This delay (where men had lain out and there was difficulty in evacuation) probably was responsible for the actual occurrence of gas gangrene in some cases; though we have no comparative figures of delayed operation cases that did not develop gas gangrene.

Bacteriology.—The diagnosis of gas gangrene, it is always admitted, must be based on clinical evidence. In 17 of these 33 cases cultures were either not taken or facilities were not available for identification of the clostridia present. In 16 cases specimens were obtained for full bacteriological examination. A piece of gangrenous muscle from the centre of the excised mass was incubated in Robertson's cooked-meat medium for 2 days, and as most of the specimens were collected in the field, the cultures were kept for some weeks before being fully studied.

Table III

Case	Interval between Wounding and 1st Operation	Onset of Gas Gangrene	Time of Death	Prophylactic A.G.G.S.
1	6 hours	7 days	14 days	22,500
2	8 hours	48 hours	72 hours	16,500
3	12 hours	4 days	—	—
4	2 hours	48 hours	—	33,000
5	14 hours	3 days	—	—
6	10 hours	3 days	—	—
7	12 hours	48 hours	—	—
8	10 hours	10 hours	—	—
9	10 hours	42 hours	48 hours	—
10	8 hours	3 days	6 days	—
11	14 hours	3 days	—	16,500
12	48 hours	48 hours	6 days	—
13	6 hours	30 hours	—	33,000
14	14 hours	48 hours	—	—
15	48 hours	48 hours	—	—
16	72 hours	72 hours	—	—
17	12 hours	48 hours	—	33,000
18	14 hours	14 hours	24 hours	—
19	48 hours	48 hours	—	—
20	48 hours	48 hours	17 days	—
21	14 hours	14 hours	22 hours	—
22	39 hours	63 hours	78 hours	—
23	16 hours	16 hours	—	—
24	12 hours	48 hours	—	33,000
25	12 hours	36 hours	5 days	49,500
26	8 hours	28 hours	—	—
27	10 hours	3 days	—	—
28	8 hours	3 days	—	—
29	4 hours	48 hours	54 hours	—
30	6 hours	5 days	11 days	49,500
31	10 hours	4 days	—	16,500
32	20 hours	8 hours	—	—
33	6 hours	24 hours	—	—

Culture plates were incubated in anaerobic pitchers which had platinized asbestos elements and some containers were made from 110-mm. shells. The predominating toxigenic clostridium was *Cl. welchii* which was isolated in pure culture from 14 of the 16 specimens, and the following criteria were accepted as diagnostic for the purposes of identification :—

1. The strains were isolated in pure culture and their morphology and cultural characters noted. Using blood-agar containing 5 per cent defibrinated human blood, the colonies were some 2 mm. in diameter and the surrounding area of hæmolysis was 1 cm. in diameter after 24 hours' incubation.

2. Stormy clot reaction in litmus milk.

3. Fermentation reactions of sugars (glucose, lactose, saccharose, and salicyn) in iron peptone water. One strain of *Cl. welchii* fermented salicyn.

4. Naglar reactions and neutralization with antitoxin. This reaction was carried out using 20 per cent plasma (citrated) in agar made from an infusion basis. Without the addition of any special peptic digest of blood, the most definite reactions were obtained. The colonies were some 3 mm. in diameter and the surrounding halo of 'precipitation' had a diameter of 8 mm. after 24 hours' incubation. The reaction was completely neutralized by the addition of 5 units of antitoxin per c.c. of culture medium. (Specific antitoxin and not a mixture of antitoxin was used.)

One clostridium was identified as *Cl. septicum* on the basis of morphology, cultural characteristics, and fermentation reactions, and was obtained from a specimen which yielded *Cl. welchii* in addition.

From two of the cultures no toxigenic clostridium was isolated in pure culture, but it appeared that *Cl. welchii* was not present.

All of the specimens contained proteolytic clostridia, and although by no means all were isolated in pure culture it appeared that *Cl. sporogenes* was much more common than *Cl. histolyticum*. There were many proteolytic clostridia which could not be identified to any degree of accuracy because they were not in pure culture or were of lesser known species.

All the specimens yielded cultures of γ-streptococci and 'coliforms'. A few yielded cultures of *Staph. pyogenes* or *Str. pyogenes*, but as the original cultures had been stored for some time at room temperature it was felt that observations relating to these could not be accepted as reliable.

Of the various methods employed to isolate *Cl. welchii* in pure culture, there could be little doubt of the value of the addition of glucose to a concentration of 0·2 per cent in Robertson's meat medium. Seven of the strains of *Cl. welchii* were isolated after only one incubation in such a medium. A liberal inoculum was introduced and subcultures made on blood-agar plates after some 6 hours' incubation. Four more strains were isolated after repeated subculture in glucose meat broth. Three strains were isolated by heating to high temperature to kill non-sporing bacteria. In this latter connexion it is of interest to note that the method was employed in an attempt to isolate *Cl. œdematiens* and *Cl. septicum* from specimens which had not yielded *Cl. welchii*. The three strains of *Cl. welchii* isolated by this method survived in a test-tube immersed in boiling water for 3 to 5 minutes. This result was unexpected (but was successfully repeated), and may have been due to the age (6 weeks) of the crude cultures which were subjected to this treatment. The strains of *Cl. welchii* were sensitive to penicillin.

Cause of Death.—There were 12 deaths. In 8 of them there were additional injuries present—penetrating wounds of abdomen and chest, fractures and soft-tissue wounds—which contributed to the fatal outcome, though the gas gangrene was the principal factor. In 5 of the 12 cases surgery for the gas gangrene was not possible or patently inadequate and all died within 24 hours from overwhelming toxæmia. But in the other 7 cases treatment had a fair start, and it is interesting to inquire why they died nevertheless:—

1. (*Case* 1.) *Secondary hæmorrhage*, 7 days after onset of gas gangrene.

2. (*Case* 10.) *Uræmia*, 3 days later. Complete suppression of urine. In the absence of other findings such as sulphonamide crystallization it was regarded as a toxic effect on the kidneys. The only sulphonamide given was 4 g. sulphadiazine 6 days before death.

3. (*Case* 20.) *Septic bronchopneumonia*, 15 days later.

4. (*Case* 21.) *Surgical shock*, 18 hours later. The other leg was also shattered and his blood-pressure never rose. In addition, toxæmia from gangrene must have contributed.

5. (*Case* 25.) *Toxic myocarditis*, 4 days later. A manifestation of the gas-gangrene toxæmia.

6. (*Case* 29.) *Toxæmia*, 6 hours later. Overwhelming toxæmia, for which the dose of antitoxin given (66,000 units) was inadequate.

7. (*Case* 30.) *Uræmia*, 10 days later. Had completed course of 18 g. sulphanilamide orally 14 days before death. Was on penicillin until the end (1,540,000 units). Became increasingly drowsy. Blood-urea 480 mg. per 100 c.c. Macroscopically the kidneys were pale and swollen, with subcapsular hæmorrhages. Microscopically there was advanced cortical necrosis, and degenerated tubules containing pigment casts (*Fig.* 88). The gas gangrene had been arrested (*Figs.* 89, 90).

GAS ŒDEMA

While the restriction of the term gas gangrene only to include clostridial myositis is an excellent working rule, it seems to us important not to lose sight of the fact that *clostridial* infection can occur and be extremely serious in *connective and areolar tissue*. By this we are not referring to what is called 'anaerobic cellulitis', which is a clostridial infection of the superficial tissues of a wound—either the subcutaneous tissues, or the muscular surface in a track. We refer to infection of deeper connective and areolar tissue, e.g., in the posterior abdominal wall or the intermuscular planes, which has always been regarded as a rare form of gas gangrene.*

The condition is characterized by œdema of fascia rather than gangrene of muscle, and there is an insidious increase in œdema until death.

* M.R.C. War Memorandum, No. 2, revised edition, 1943.

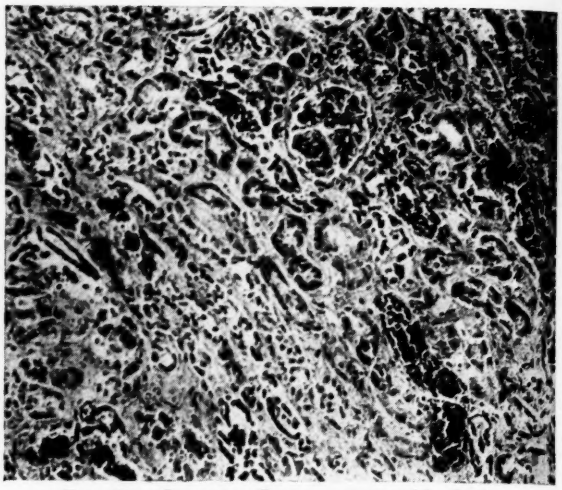

FIG. 88.—*Case* 30. Gas gangrene, with death on tenth day from renal failure. Cortex of kidney, showing extensive degeneration of convoluted tubules. Pigment casts present. (× 25.)

FIG. 89.—Same case. Formation of tissue reaction barrier. Zone of polymorphonuclear leucocytes at the edge of gangrenous muscle. (× 25.)

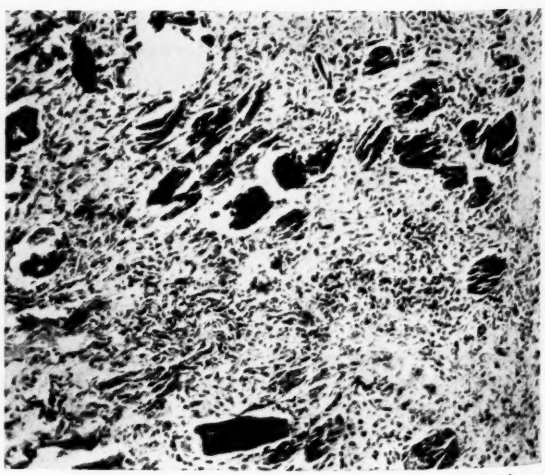

FIG. 90.—Same case. Formation of fibroblastic connective tissue, with macrophages removing muscle debris. (× 25.)

Clinically it resembles anaerobic streptococcal infection, or myositis due to *Cl. œdematiens*—the œdema, the rather insidious course, the relatively normal temperature. An example of this gas œdema, or clostridial fasciitis, follows :—

Case 34.—Gdsm. L., aged 33.

Feb. 14.—Shell wound perforating right foot, with fractured tarsal and metatarsal bones.

Feb. 15.—*Operation* : Casualty Clearing Station (24 hours after wounding). Large ragged wounds on dorsal and plantar surfaces of foot excised. Penicillin-sulphathiazole powder insufflated. Plaster splint.

A.G.G.S., 16,500 units intravenously.

Feb. 19.—Admitted to General Hospital General condition good. Foot cold and insensitive.

Feb. 24.—Complaining of pain in foot and leg. Patient not apparently toxic. Temperature 99° F. Pulse 94. Foot and whole of leg markedly œdematous.

Operation : Amputation through mid-thigh. There was œdema of subcutaneous and connective tissues in thigh, but no myositis. (The amputated leg showed connective-tissue œdema, but the muscles appeared normal. No gas.)

Culture : *Foot*, Gram-positive spore-bearing clostridia. *Thigh*, no growth.

A.G.G.S., 60,000 units intravenously at operation. Course of intramuscular penicillin started—15,000 units intramuscularly 3-hourly.

Feb. 24–28.—540,000 units penicillin. Well-marked improvement in general condition.

March 2.—Stump dressed. Healthy, and the flaps were loosely approximated. Culture, scanty growth of cocci.

March 4.—Rapid onset of œdema of thigh and deterioration in general condition. Temperature 98·6° F. Pulse 120.

A.G.G.S., 60,000 units intravenously. Plasma, 5 pints.

Culture from stump : Gram-positive bacilli.

March 5.—Died.

POST-MORTEM EXAMINATION.—Nil to note except marked œdema in connective tissues of thigh.

Comment.—This appeared to be a clostridial infection of connective tissue, without myositis. Unfortunately the bacteriology was not fully worked out.

COMMENTARY

The two most striking features in this series were, first, the arrest of the gangrenous process ; and, secondly, the late ill effects that occurred after the men appeared to be recovering from gas gangrene. The arrest of the progressive myositis in almost every case was probably due to the effect of penicillin on the infecting clostridia. By thirty-six hours at the outside there was no further advance of gangrene, and histological section at the barrier area showed the connective tissue reaction of a healing process. Between gangrenous muscle on the one side and healthy muscle on the other, there was a definite zone of fibroblastic connective tissue reaction, with infiltrating lymphocytes and macrophages.

Nevertheless, in spite of the arrest of the gangrenous process, several men died later, and of these the most interesting were the cases of renal failure. The kidney changes were not dissimilar to those described in the crush syndrome, with tubular degeneration and pigment deposit, but with cortical necrosis added. These changes may have been due to multiple blood transfusions, but were more likely toxic effects from the retained degenerated and autolysing muscle.

The over-all mortality in this penicillin-treated series was 36 per cent. In making any comparison between this and previous mortality figures in Italy it must be borne in mind that the surgeons concerned were becoming more experienced, and any improvement must be attributed in part to their increasing education. To a lesser extent, the same applies to another comparison that can be made between the cases in this series which received full treatment (25 per cent mortality) and the cases from Sicily and Italy reported by J. D. MacLennan and M.G. Macfarlane (1944). Thirty-five of their cases received what they describe as Class I treatment, i.e., early surgical treatment, antiserum, and sulphonamide chemotherapy ; the mortality was 34 per cent.

Given fair conditions, and with penicillin, we may hope to see the mortality from gas gangrene in the Field reduced to the region of 20 per cent. We do not anticipate that it will ever be much lower because of the additional injuries unconnected with the gas gangrene and the ' untoward ' late fatalities. Nor can we expect to save many of the rapid fulminating cases that cannot come to surgery : " *Contra vim mortis non est medicamen in hortis* ".

SUMMARY

1. Penicillin has a definite place alongside surgery and antiserum in the treatment of gas gangrene.

2. In 33 cases of gas gangrene the mortality was 36·4 per cent, though the prognosis was significantly better when adequate surgery was possible.

3. The arrest of the progressive myositis does not remove all danger to life. Late effects must be anticipated and if possible guarded against.

4. *Cl. welchii* is the usual causal organism of gas gangrene in Italy.

This was a report submitted to the Director of Pathology, the War Office, by the Penicillin Control Unit, C.M.F. Our thanks are due to Major-General L. T. Poole, D.S.O., M.C., for advice and for permission to publish this report ; to Administrative Officers and Surgeons in Italy for their full co-operation ; to Major J. D. MacLennan for help in the Field initially ; to Major G. H. Eagles for assistance in the isolation of the anaerobes ; to Major W. E. Hamilton and Dr. Joan Ross for pathological examinations ; and to Mr. P. G. Hennell for photography.

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TREATMENT OF CLOSTRIDIAL INFECTIONS WITH PENICILLIN

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Gas gangrene is one of the most serious and dreaded complications of war wounds. Recent reports from Allied Forces in the Mediterranean reveal that the incidence and the mortality-rates for troops fighting in Continental Europe are practically the same as those occurring in our Forces in 1914–18. All agents, whose use in such cases offers hope, must receive careful scrutiny.

Penicillin *in vitro* exhibits a bacteriostatic effect upon the organisms frequently associated with gas gangrene (Chain et al., 1940; Hobby et al., 1942, a). *Cl. welchii* and *Cl. septicum* infections experimentally produced in laboratory animals have been successfully treated as well as prevented by this agent when it is administered before, at the time of, or shortly after, inoculation with the organisms concerned (Chain et al., 1940; Hac and Hubert, 1943; McIntosh and Selbie, 1942, 1943, a).

Reports in the medical literature on the use of penicillin in clinical gas gangrene have not been numerous. Pulvertaft (1943) describes one case of gas gangrene in his article dealing with local therapy in war wounds. A patient who developed a clostridial infection following severe wounding recovered after local application of the drug. Experience with the use of penicillin for the treatment of gas gangrene in the British Forces in Africa have been reported by Florey and Cairns (1943). Seven cases, all *Cl. welchii* infections, were treated with sodium penicillin parenterally; 4 recovered and 3 died. However, in two of the fatal cases the clostridial infection appeared to have been overcome at the time of death. Among the 4 cases which recovered, 2 were severe, 1 was limited to a single muscle, but was localized and had the appearance of anaerobic cellulitis. In this report it was pointed out that penicillin did not counteract the toxæmia of gas gangrene and that all dead muscle should be removed and massive doses of gas-gangrene antitoxin should be given. McNight, Loewenberg, and Wright (1944) describe a case of gas gangrene in a child occurring after compound fractures of the forearm. Recovery from what seemed a hopeless outcome is attributed to the use of penicillin parenterally.

Experience with penicillin therapy for clostridial infections in American hospitals in the European theatre of operations has been limited. Nevertheless, because of current interest both in the agent and in the infection, detailed descriptions of 7 cases of gas gangrene treated with penicillin will be presented.

CASE REPORTS

Case 1.—C. M., aged 20, was wounded in aerial combat by a rocket shell which exploded near his plane. The greater part of the musculature of the posterior right thigh was blasted away, a segment of the sciatic nerve was destroyed, and there was a compound comminuted fracture of the middle third of the femur. The large vessels, however, were intact. There was also damage to the posterior surface of the left thigh. This was extensive and involved the destruction of a considerable part of the hamstring muscles; the left sciatic and the large vessels were not disturbed and there was no fracture (*Fig.* 91).

Fig. 91.—*Case* 1. Taken approximately 12 hours after wounding, and showing extensive destruction of the tissues, particularly muscle, of both posterior thighs.

The patient arrived at the hospital exsanguinated and in profound shock. He was transfused with large amounts of plasma, as well as 1500 c.c. of whole blood, and rallied sufficiently to permit operation. There was, however, a necessary time interval of 12 hours between injury and operation.

The operation consisted of a thorough débridement of the right thigh wound including the compound fracture. The wound of the left thigh was also débrided, but on account of the poor condition of the patient, the débridement was incomplete. The fracture was treated by suspension and traction by means of a Kirschner wire which had been passed through the tibia crest before débridement was started.

Penicillin in saline solution was sprayed and instilled into both wounds, each receiving 10,000 units. He was started on intramuscular penicillin, 10,000 units every three hours. Next day the patient's serum was definitely bacteriostatic for the standard staphylococci (Oxford H strain) three hours following the administration of penicillin. Another satisfactory result from a bacteriostatic test was obtained the second day following operation.

During the first two days succeeding operation there were several unsustained elevations in pulse and temperature, the greatest being 128 and 102·8° F. respectively. He was restless and appeared quite

ill. These findings, however, were not thought to be out of proportion to the magnitude of the original injuries. At about 50 hours after operation he complained of pain in the right lower extremity. A radiograph taken approximately 60 hours postoperatively to determine the position of the bone in the right thigh revealed the presence of gas in the tissues. The wound was then inspected and necrotic muscle and a small amount of gas were found. Smears taken showed a great number of Gram-positive rods with subterminal spores.

Because of the diagnosis of clinical gas gangrene involving such a large group of muscles, and in view of the extensive bone damage and division of the sciatic nerve, amputation was decided upon. This was carried out at the site of the fracture although the bone was cut across at a slightly higher level. The entire

FIG. 92.—Same case, taken 14 days following amputation.

mid-portion of the hamstring group of muscles was involved in an extensive necrotic process which in several areas had progressed to liquefaction.

The open stump was sprayed with 20,000 units of penicillin, and the parenteral dosage was increased from 10,000 units to 20,000 units every three hours. Following operation 100,000 units of bivalent (*Cl. welchii* and *Cl. septicum*) gas-gangrene antitoxin were given intravenously. The same dosage was repeated on the first, second, and fourth days after amputation.

On the second day following amputation additional necrotic muscle appeared on the end of the stump and was cut away. Thereafter the wound surface showed no evidence of clostridial infection and healthy granulations rapidly appeared.

Although débridement of the wound of the left thigh was far from complete at the time of the initial operation, and clostridia were cultured from its surface, no clinical manifestation of a clostridial infection developed on this side. At the time of the amputation on the right, a secondary débridement was performed on the left, with removal of dead tissue and numerous pieces of blue woollen flying suit.

The organism causing the infection on the right was an anaerobic Gram-positive bacillus with subterminal spores. Stormy fermentation was produced in iron milk. It is not sensitive to penicillin. It has not been further classified. That it is a member of the clostridial group appears certain.

Following amputation the patient showed no febrile episodes save those associated with reaction to intravenous serum therapy. He was transfused frequently, skin traction was maintained along the amputation stump, and his course was one of continued progress (*Fig.* 92). He was transferred to a general hospital 22 days following original injury.

Comment.—This appears to be a typical case of clinical gas gangrene that did well following amputation. The role of penicillin in this case is doubly hard to evaluate since the clostridium was insensitive to penicillin. The presence of clostridia in the left thigh wound without clinical evidence of gas gangrene should be noted.

Case 2.—W. E., aged 24, was wounded in aerial combat by a 20-mm. shell. There was a compound, complete, extensively comminuted fracture of the left tibia and fibula at the junction of the upper and middle thirds. Damage to soft parts was extensive, involving skin, subcutaneous tissue, portions of the tibialis anticus, peroneus profundus, and peroneus longus muscles. A segment of the peroneal nerve was lost.

He was admitted in profound shock, from which he recovered after 1400 c.c. of plasma and 1000 c.c. of whole blood were given. During operation another 1000 c.c. of blood were administered. Operation under pentothal anæsthesia was started approximately 12 hours after wounding. A narrow margin of skin and all devitalized muscle were cut away. The wound was irrigated with physiological saline solution and 10,000 units of penicillin in 20 c.c. of saline solution were sprayed on the surface. The wound was left open and a loose vaseline gauze dressing put on it. The leg was placed on a Braun splint and traction applied through a Kirschner wire previously inserted in the os calcis.

Immediately after operation penicillin, 10,000 units, given intramuscularly every three hours, was started. On the second day of administration the activity of the penicillin in the patient's serum was tested against the standard staphylococcus. A bacteriostatic effect was demonstrated three hours after intramuscular administration of 10,000 units.

Frequent transfusions of whole blood were given throughout hospitalization. During the first two days the temperature ranged between 100° F. and 102° F. and the pulse-rate remained below 110. Dressings were stained reddish yellow, but not until 52 hours after operation was an offensive odour noted. The wound was dressed and there was clinical evidence of gas gangrene, involving the tissues distal to the open wound (*Fig.* 93). The muscles in the proximal part of the wound looked normal.

Operation was performed under pentothal anæsthesia. The skin of the anterior aspect of the leg was opened from the tubercle to the ankle (*Fig.* 94). The tibialis anticus and the peronei from their bellies to their tendinous insertions had undergone changes varying from simple injection to ischæmia and complete autolysis. Every bit of involved muscle was excised. Twenty thousand units of penicillin were placed in the wound and the parenteral dosage was increased from 10,000 to 20,000 units every three hours. This was continued until a total of 1,050,000 units were given.

Immediately after the second operation 100,000 units of polyvalent gas-gangrene antitoxin were given intravenously. These amounts were repeated on the first and third days following operation.

On the first post-operative day a small amount of superficial necrotic tissue was cut away and 20,000 units of penicillin in saline solution applied locally. Thereafter, the wound showed no evidence of gangrene and soon was covered with healthy granulations (*Fig.* 95) upon which surface small deep grafts were placed with complete success (*Fig.* 96). Once the wound was well epithelialized, a long leg cast was applied.

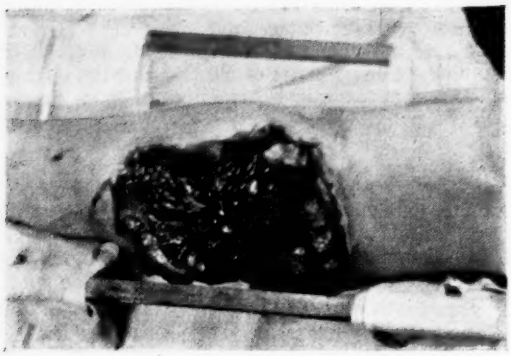

FIG. 93.—*Case* 2. Taken at the time of discovery of gas gangrene. Note the discoloration of the muscles in the distal portion of the wound. There is no gangrenous involvement of those in the upper half of the wound.

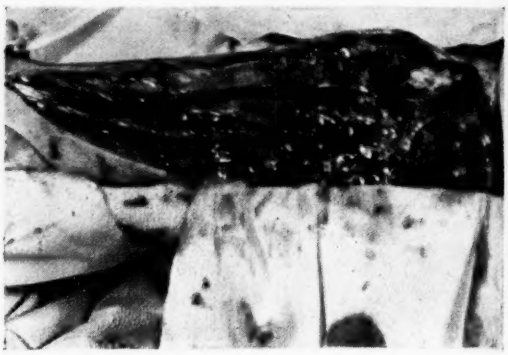

FIG. 94.—Same case, taken at time of operation for gas gangrene. Note the extensive incision necessary to remove the invaded muscles.

FIG. 95.—Same case, taken approximately one week after operation. Note that much of the wound is covered with healthy granulations.

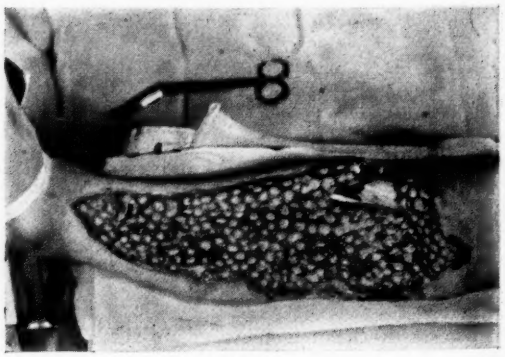

FIG. 96.—Same case. Skin-grafts have covered almost the entire wound.

Three organisms were isolated from the involved tissue: A Gram-positive anaerobic bacillus producing stormy fermentation in iron milk, and which is probably *Cl. welchii*, *Cl. tetanomorphum*, and a Gram-positive coccus. The first one was as sensitive to penicillin as the standard staphylococcus.

The patient has been transferred to a general hospital and accounts of progress are satisfactory, but at the time of this report it is too early to evaluate the final bone healing and functional result.

Comment.—This case exemplifies clostridial myositis confined to a group of muscles. The organism was sensitive to penicillin. Local surgical extirpation gave a good result. Here penicillin may have been of therapeutic value, although its use early did not prevent progressive invasion with a clostridium.

Case 3.—A. T., aged 30, was wounded by flak while engaged in aerial combat. He sustained a perforating wound of the lateral aspect of the right upper thigh associated with a compound fracture of the right femur. The wound of entrance was above and posterior to the greater trochanter; the wound of exit was 8 cm. above and lateral to the knee; the track was 30–40 cm. long. Muscle was markedly damaged, but the major vessels were intact. He had been given 750 c.c. of plasma at the airfield and reached the hospital in good condition. Prior to and during operation, 1000 c.c. of whole blood were given.

Operation, consisting of débridement, was performed seven hours after injury. The wounds of entrance and exit were enlarged and the tract débrided. A pin was inserted through the tibial crest and the fracture was reduced by skeletal traction. The wounds were left open and 75,000 units of sodium penicillin powder mixed with 6 g. of sulphanilamide were applied locally. Intramuscular administration of penicillin in doses of 20,000 units every three hours was started.

Within the first forty-eight hours following operation the temperature rose to 101·6° F. and much serous material stained the dressings. Approximately sixty hours after débridement a dressing was done under pentothal anæsthesia. There was a suggestive odour of decay. When the site of fracture was exposed by means of retractors several bubbles of gas were noted. All visible muscle in the upper wound looked healthy. The tissue surrounding the fracture site was discoloured, but otherwise unchanged. The area was thought to be a potential site for a clostridial

infection. A portion of muscle was excised for bacteriological examination, and it was decided to await culture report before proceeding further. The next morning stormy fermentation of iron milk was noted in the culture from the upper wound, but not from the lower. The wound was then explored under anæsthesia. Pale, swollen, friable, and discoloured muscle was noted. There was no crepitus, nor was the skin changed. The process was limited to the site of the fracture and to the upper third of the vastus lateralis muscle. Scattered throughout this segment of muscle were areas of necrosis and liquefaction apparently isolated from the original wound. All devitalized tissue, i.e., an area approximately 12 cm. × 12 cm. × 4 cm., was excised and 75,000 units of sodium penicillin in 6 g. of sulphanilamide were placed in the wound.

The day before the second operation 150,000 units of polyvalent gas-gangrene antitoxin were given intravenously and sulphadiazine was started by mouth. Antitoxin in doses of 100,000 units was repeated two and four days later. Sulphadiazine was continued in 1-g. doses every three hours until the fifth day after the second operation.

The penicillin dosage was unchanged and 160,000 units were given daily for the first nine days after the initial débridement. Forty-eight hours after the second operation 100,000 units of penicillin in 8 g. of sulphanilamide were placed in the wound. Local therapy was continued for another four and a half days. This was accomplished by instilling, through a rubber tube, 4000 units of sodium penicillin dissolved in 4 c.c. of saline, into the wound every three hours.

Culture of the tissue débrided at the original operation revealed a pure growth of *Cl. welchii*, sensitive to penicillin. The same organisms in mixture with staphylococci were grown from the established infection. On the seventh day of penicillin therapy the patient's undiluted serum obtained three hours after an intramuscular dose produced complete bacteriostasis of the test staphylococcus.

Forty-eight hours after the second operation the wound was free from odour and dead tissue, and two days later it was covered with healthy granulation. The patient's course has been uneventful. He is afebrile and remains in hospital at the time of this report.

Comment.—This is another example of localized clostridial myositis. In this case the organism was penicillin-susceptible. The continued development of clostridial invasion with a penicillin-susceptible organism leads us to place a greater weight on the successful therapy of the second surgical operation than upon penicillin.

Case 4.—C. H., aged 22, was injured in an airplane crash. He sustained a complete traumatic amputation of the left lower leg at the junction of the middle and lower thirds, a compound comminuted fracture of the right os calcis and astragalus, with anterior dislocation of the ankle and avulsion of the Achilles tendon, and a simple fracture of the right tibia and fibula. The injury caused much destruction of tissue and there was marked soiling with dirt and vegetation. He had been given 500 c.c. of plasma at the airfield and was in good condition when admitted to the hospital, where he was transfused with 500 c.c. of whole blood.

Operation was performed within four hours after receipt of injury. It consisted of débridement of both wounds. The fractured ankle was immobilized in plaster and traction was applied to the fractured tibia and fibula by means of a pin inserted in the lower tibia and incorporated in this cast. Both wounds were left open and 15,000 units of penicillin were placed in the amputation stump and 25,000 units in the right ankle wound. Intramuscular penicillin in amounts of 20,000 units every three hours was started. The débrided tissue from each of the wounds was cultured and showed the presence of *Cl. welchii* and *Cl. sporogenes*. The former was sensitive to penicillin.

Within twenty-four hours after operation the temperature was elevated to 101·4° and the pulse-rate was 120. Because of these signs and the presence of clostridial wound contamination 100,000 units of polyvalent gas-gangrene antitoxin were given intravenously and oral sulphadiazine was started. The febrile state continued and by 48 hours after injury signs of bilateral gas gangrene were unmistakably present. The infection on the left was localized to the distal 2 cm. of the cut soleus muscle. This was dark brown in colour and avascular. Odour of decay was present. The diseased part of this muscle was excised and 50,000 units of sodium penicillin powder in 4 g. of sulphanilamide were placed into the wound. The muscles of the sole of the right foot (flexor digitorum brevis, adductor digiti quinti) were ischæmic, necrotic, and partially liquefied. Treatment here consisted of a guillotine amputation at the site of the fractured tibia and fibula, which proved well above the involved area. Fifty thousand units of dry penicillin powder in 4 g. of sulphanilamide were placed into the wound. *Cl. welchii* and *Cl. sporogenes* were cultured from both infected wounds.

The intramuscular dosage of penicillin was increased to 40,000 units every three hours. A bacteriostasis test against the standard staphylococcus done the day following the development of gas gangrene showed satisfactory levels in the undiluted serum three hours following intramuscular administration of 40,000 units of penicillin. Penicillin therapy was continued for a period of eight days following the original operation and the total quantity given both locally and parenterally amounted to 2,080,000 units. Following the operations for gas gangrene, polyvalent gas-gangrene antitoxin was administered intravenously each day until 460,000 units had been given. Thirty-four grammes of sulphadiazine were given orally over a period of four days. He was transfused frequently with whole blood, a total of 3500 c.c. being given during the first eight days of hospitalization.

Progress was highly satisfactory and once transfusions and antitoxins were stopped he became afebrile. The infection remained completely controlled, and by the twelfth day after the operations for gas gangrene the wounds were completely covered with healthy granulation tissue.

Comment.—This case evidences bilateral gas gangrene following extensive injury. The clostridium involved was penicillin-susceptible, yet it was able to invade and progress in spite of the presence of penicillin. Unquestionably surgery played the dominant role in therapy, but the penicillin and gas-gangrene antitoxin may have been of assistance.

Case 5.—D. W., aged 21, sustained, in a motor-cycle accident, a compound fracture of the shaft of the right femur at the junction of the middle and lower thirds. Six inches of the upper fragment projected anteriorly through a large gaping wound which was grossly soiled. Tissue destruction was extensive. In addition to the femoral fracture, there was a compound comminuted fracture of the mid-shaft of the right tibia. The right fibula was not fractured. The foot was cold and pale, and no pulsation could be felt in the posterior tibial or dorsalis pedis arteries.

He was given 1200 c.c. of plasma and 500 c.c. of whole blood, and within three hours after injury operation was performed. This consisted of careful débridement of both wounds and reduction of the fracture. Sodium penicillin in saline solution was introduced into each wound, 15,000 units in the femoral and 5000 units in the tibial, and vaseline gauze dressings were loosely applied. Shortly after operation a lumbar sympathetic block failed to improve the circulation of the right lower extremity.

Immediately following operation, intramuscular penicillin in doses of 10,000 units every three hours was started. This amount proved satisfactory for bacteriostasis of the standard staphylococcus when the patient's blood-serum was tested three hours after an intramuscular dose.

The patient remained febrile, and on the third post-operative day considerable swelling of the leg and thigh, some areas of bluish-grey discoloration of the skin, and slight crepitus were detected. A diagnosis of gas gangrene was made, but smears were negative. Cultures taken at the same time yielded on the next day an anaerobic Gram-positive bacillus which produced stormy fermentation in iron milk. This was thought to be *Cl. welchii*. By this time the clinical evidence of gas gangrene was unmistakable. The thigh muscles showed changes varying from ischæmia to purple discoloration. Some areas were friable, necrotic, and even liquefied. A circular guillotine amputation was done at the site of the femoral fracture.

The amputation stump was sprayed with 10,000 units of penicillin solution. The parenteral dose had been increased to 20,000 units every three hours the day preceding, and was continued until the fourth day following operation. By this time a total of 1,120,000 units had been given. Once the diagnosis of gas gangrene had been established bivalent antitoxin (*Cl. welchii* and *Cl. septicum*) was administered in doses of 67,500 to 155,000 units, until a total of 457,500 units had been given.

After amputation his general condition became fairly satisfactory, but from the amputation stump gangrene extended up the adductor group of muscles, and 48 hours after amputation these muscle bundles were dissected out and removed at their origin. Following this procedure there was prompt general and local improvement, and as early as 72 hours after the last operation no clostridia could be cultured from the wound. Thirty-five days following the injury he was transferred to a British hospital.

Comment.—This was a road accident. Penicillin treatment was begun early and yet by the third post-operative day clinical gas gangrene was well established, and though penicillin therapy was continued it required both an amputation and a secondary muscle excision operation to relieve the patient of his clostridial invasion. Certainly there is no evidence here of great benefit from the use of penicillin.

Case 6.—K. C., aged 22, was injured in an airplane landing accident while returning from an operational mission. He sustained bilateral compound comminuted fractures of the tibia and fibula, a complete compound comminuted fracture of the lower third of the left femur, simple fractures of the right radius and right femur, and severe cerebral contusion manifested by aphasia and partial hemiplegia.

Upon admission to the hospital there was evidence of considerable blood-loss and severe shock. The multiple compound fractures of the right lower leg and left femur were splinted and dressed. In spite of treatment for shock and hæmorrhage he failed to improve. Both legs showed evidence of marked circulatory impairment, and bilateral amputation was deemed necessary as a life-saving measure. Upon removal of splints and dressings, twenty-three hours after the injury, gas bubbled from both of the compounded wounds in the lower legs. A diagnosis of gas gangrene was made based on odour of decay, swelling, discoloration of muscles, and crepitation. Bilateral guillotine amputations were performed on the left at the level of the fractured femur; on the right at the level of the compound fractures of tibia and fibula.

Post-operatively intravenous sulphadiazine was started and 10 g. were given during the first 24 hours, after which time it was discontinued and penicillin therapy begun. This was given in three-hourly intramuscular doses of 20,000 units of the sodium salt. After three days this dosage was reduced, but the drug was continued over a period of 13 days, during which time approximately one million units were used. Twice penicillin (20,000 units) was instilled on the amputation stumps. On other occasions vaseline gauze, azochloramide, or eusol dressings were used.

By the fourth day following amputation the temperature was normal and his convalescence was good, the wounds healed most satisfactorily, and there was no complication. He was transferred to a general hospital in the zone of the Interior.

Cultures taken from both stumps at operation yielded anaerobic organisms of the clostridial group which produced digestion of milk, but which could not be further identified. This organism was extremely sensitive to penicillin.

Comment.—In this case there was severe trauma. The presence of clostridia was demonstrated, but bacteriostatic tests were not done and penicillin was administered relatively late. Although penicillin therapy may be considered inadequate, the healing after careful surgery was rapid and as satisfactory as in the preceding cases where penicillin was begun early and carried on in greater dosage.

Case 7.—L. K., aged 23, was wounded in aerial combat by 20-mm. shell fragments. There was a compound comminuted complete fracture of the left femur at the junction of the middle and lower thirds, with an associated perforating wound of the thigh at this level. There was a compound fracture of the right femur in the lower third, incomplete, and comminution, though present, was minimal.

The patient was in severe shock and 1450 c.c. of plasma as well as 1500 c.c. of whole blood were given before he was ready for operation. Twelve hours intervened between wounding and operation. Under pentothal induction and nitrous-oxide–ether anæsthesia the entrance and exit wounds on each extremity were débrided, irrigated with physiological saline solution, and closed by suture. No chemotherapeutic agent was used either locally or parenterally. Kirschner wires were inserted through the left tibial crest and the lower left femoral fragment. The fractures were reduced and position maintained by skeletal traction on the left and by skin traction on the right.

From the very beginning the patient was quite drowsy but could be roused easily. The first post-operative day temperature rose to 102·6° F. and the pulse-rate was 136. Approximately 36 hours after operation cultures from the tissues excised at the primary operation from both thigh wounds showed stormy fermentation in iron milk; because of this

finding the wounds were dressed. Those on the right were clean. The dressings on the left were stained with a sero-sanguinous discharge which had an offensive odour. Gas bubbled from between the sutures of the lateral wound when the dressings were removed. The thigh was tense, swollen, and the lateral aspect was discoloured. The left medial wound showed slight swelling and slight discharge with odour. Both wounds were opened and smears revealed large numbers of Gram-positive rods.

Based on these findings a diagnosis of gas gangrene was made and a circular mid-thigh amputation through the site of fracture was performed under nitrous-oxide-ether anæsthesia. Gas, sero-sanguinous exudate, and devitalized, pale, fragmented muscle showing autolysis were noted. The process was sufficiently well localized to make possible the removal of all diseased tissue. The stump was left open and 100,000 units of sodium penicillin mixed with dry plasma insufflated.

Following amputation he was transfused with 500 c.c. of whole blood. He was given gas-gangrene antitoxin (100,000 units *Cl. welchii* antitoxin; 100,000 units *Cl. septicum* antitoxin; 30,000 units *Cl. histolyticum* antitoxin; 15,000 units *Cl. œdematicus* antitoxin; 15,000 units *Cl. sordellii* antitoxin) intravenously, and started on the sodium salt of penicillin intramuscularly. Twenty-thousand units of penicillin were given at two-hour intervals for four and a half days, making a total parenteral dose of 1,100,000 units. Penicillin bacteriostasis test on the third day after amputation showed complete bacteriostasis of the test staphylococcus in a 1 : 1 dilution of patient's serum two hours after penicillin had been given. Forty-eight hours after amputation one-half of the aforementioned dosage of gas-gangrene antitoxin was given.

The day of amputation his temperature was 103° F., the next day the highest was 99° F., and on the day succeeding it dropped to normal, where it remained. During the first 24 hours in the hospital his urinary output was normal, but thereafter it was suppressed and not concentrated. Urea nitrogen three days following amputation was 40 mg. per cent, non-protein nitrogen 150 mg. per cent, and blood-urea 85·7.

The wound was dressed the day after amputation and again in two days. On both occasions it was clean and no evidence of gas gangrene was present. There was moderate serosanguinous discharge, without odour, and the muscle everywhere was red and contractile. At the first dressing the wound surface was insufflated with 50,000 units of penicillin in plasma.

He continued to be lethargic but not comatose, to have reduced urinary output, and, five days following amputation, died. On the day of death urea-nitrogen was 57 mg. per cent, non-protein nitrogen 171 mg. per cent, and blood-urea 132. Repeated examinations failed to show pulmonary or peripheral œdema until six hours before death.

The organism producing the infection has been identified as *Cl. welchii*. Also isolated were a hæmolytic *Staph. aureus*, coagulase-positive and not sensitive to penicillin, and hæmolytic streptococcus.

At post-mortem examination pale swollen kidneys were found. The renal capsule stripped easily, but on cross-section the normal demarcation between cortex and medulla was not distinct. Microscopical examination showed dilated and moderately degenerated proximal convoluted tubules. Numerous ascending loops of Henle and distal convoluted tubules were dilated and contained hæmoglobin-like casts. Several tubulovenous aneurysms were seen at the corticomedullary junction. In many glomeruli the subcapsular space contained a reticular coagulum which extended into the proximal convoluted tubules. Many accumulations of round cells were seen throughout. In addition to the renal findings, there were central necrosis of the liver and acute diffuse pancreatitis.

Comment.—This is a patient with bilateral compound fracture of femora with fatal outcome. Clostridia were demonstrated in both wounds, but clinical gas gangrene only developed on one side. Early amputation (36 hours) seemed, clinically, to rid this patient of his infection. The post-mortem findings are those seen in fatalities after trauma, both with and without infection. Possibly the crush syndrome played a part since the renal disability was the predominant factor in the fatal outcome. Penicillin, as in *Case* 6, was not used prophylactically, and seems to have played no important role in this case.

DISCUSSION

The essential data from the 7 cases reported herein are presented in *Table I*. We feel that each one of these patients had definite clinical gas gangrene, Moreover, clostridia were recovered from the involved tissues in each instance. Compound fracture associated with considerable bone damage and maceration of soft tissues, particularly muscle, was present in every patient. In 2 (*Cases* 5 and 6) there was marked vascular damage. All had bled extensively and all by 2 (*Cases* 3 and 4) arrived at the hospital in profound shock.

Five patients (*Cases* 1–5) were given penicillin from the very time of the primary operation in what appeared to be adequate parenteral and local doses. Administration of penicillin was continued after the recognition of the clostridial infection. Each one of these patients recovered and in 2 (*Cases* 2 and 3) it was possible to save the involved extremities.

The drug was not started in 2 patients (*Cases* 6 and 7) until after the onset of the clostridial invasion. One of these (*Case* 6), who could not be given adequate surgery due to profound shock, was simply dressed and splinted. He developed gas gangrene in both legs within 24 hours after injury, but did perfectly well following bilateral amputation. It is difficult to evaluate the therapeutic role of penicillin in this case since administration of it was not begun until 24 hours after the amputations. The other patient (*Case* 7) also developed gas gangrene early, within 36 hours after injury. Amputation was necessary, but uræmia ensued and the patient died 5 days following the operation. At the time of death the local clostridial infection appeared to have been controlled. Microscopically the kidneys showed hæmoglobinuric nephrosis.

While it is unwise to draw conclusions from so small a group of cases, we are impressed with the fact that out of 7 cases of gas gangrene, only 1 proved fatal and 2 recovered without loss of limb.

Equally impressive is the fact that of the recovered cases in no instance was a fatality

Table I.—SUMMARY OF CASES

Case No.	Injury	How Incurred	Initial Operation	Shock	Interval in Hours between Injury and Operation	Culture of Débrided Tissue at Initial Operation	Prophylactic Penicillin		Prophylactic Gas Gangrene Antitoxin
							Locally	Intramuscularly	
1	Compound comminuted fracture, femur. Marked maceration of muscle	Aerial combat. Rocket	Débridement and irrigation, wound left open	Profound	12	No culture	10,000 units	10,000 units every 3 hr.	None
2	Compound comminuted fracture, tibia and fibula. Tibialis anticus muscle severed	Aerial combat. 20-mm. shell	Débridement and irrigation, wound left open	Profound	12	No culture	10,000 units	10,000 units every 3 hr.	None
3	Compound comminuted fracture, femur. Marked maceration of muscle	Aerial combat. Flak	Débridement and irrigation, wound left open	Moderately severe	7	*Cl. welchii*	75,000 units and 6 g. sulphanilamide	20,000 units every 3 hr.	None
4	1. Compound comminuted fracture, os calcis and astragalus, right 2. Traumatic amputation, lower leg, left	Crash-landing	Débridement and irrigation, wounds left open	Moderately severe	4	*Cl. welchii*. *Cl. sporogenes* from both wounds	1. 15,000 units 2. 25,000 units	20,000 units every 3 hr.	100,000 units polyvalent 28 hr. after débridement
5	Compound comminuted fracture, femur. Blood-supply to lower extremity impaired	Motor accident on highway	Débridement and irrigation, wound left open	Profound	3	No culture	15,000 units	10,000 units every 3 hr.	None
6	1. Compound comminuted fracture, femur, left. 2. Compound comminuted fracture, tibia and fibula, right. Circulation to both lower extremities impaired	Crash-landing	No débridement	Profound	No operation	No culture	None	None	None
7	Compound comminuted fracture, femur. Marked muscle destruction	Aerial combat. 20-mm. shell	Débridement and irrigation, primary closure of wound	Profound	12	*Cl. welchii*. Streptococcus. Hæmolytic *Staphylococcus aureus*	None	None	None

apprehended. Each of the 7 patients had the benefit of early diagnosis, prompt surgical extirpation of the infected tissue, therapeutic penicillin, large amounts of gas-gangrene antitoxin, and frequent blood transfusions. With so many factors tending to influence the outcome, it is difficult to estimate the value of any single one. Our impressions as to the evaluation of therapy have been entered under the comments following each case report.

For the group as a whole, one conclusion is obvious and outstanding: Penicillin used prophylactically in the manner herein described did not prevent the development of gas gangrene. The role of this agent in modifying and altering the infection or in combating secondary invaders cannot be properly assessed on the basis of the limited number of cases and the lack of a comparable group of control cases treated by other methods.

There can be little doubt but that penicillin is effective against many of the organisms which are found amongst the multiple contaminants in the wounds of battle casualties. Also, a reduction in the devitalizing and even destructive effects of such other organisms tends to prevent a suitable medium for growth of the clostridia. At the same time this small experience does not fall in line with published and confidential reports to us that "penicillin is extremely effective in gas gangrene."

The development of gas gangrene in the wounds of aerial warfare may seem somewhat surprising. Six of these infections occurred in air-force personnel; 4 were wounded during missions over enemy territory and 2 were injured

UMMARY OF CASES REPORTED.

Surgical Treatment for Clostridial Infection	Therapeutic Gas Gangrene Anti-toxin	Therapeutic Penicillin			Satisfactory Penicillin Blood-Level		Culture of Infected Tissue	Clostridium Penicillin-sensitive	Amputation	Result	Remarks
		Locally	Intramuscularly	Total	Prophylactic	Therapeutic					
Amputation. 48 hr. later, necrotic muscle excised	400,000 units bivalent	20,000 units one time	20,000 units every 3 hr.	1,120,000 units	Yes	Yes	Clostridium. Gram-negative bacilli	No	Yes	Recovery	
Excision of tibialis anticus and peronei muscles	300,000 units polyvalent	20,000 units twice	20,000 units every 3 hr.	1,050,000 units	Yes	Yes	Clostridium (*Welchii* ?). *Cl. tetanamorphum*. Gram-positive cocci	Yes	No	Recovery	
Excision of portion of vastus lateralis muscle	350,000 units polyvalent	*a*, 75,000 units one time. *b*. 4000 units every 3 hr. for 4½ days	20,000 units every 3 hr.	1,660,000 units	Not done	Yes	*Cl. welchii*	Yes	No	Recovery	
Amputation, right foot. Excision of portion of soleus muscle, left	460,000 units polyvalent	50,000 units in each wound	40,000 units every 3 hr.	2,080,000 units	Not done	Yes	*Cl. welchii*. *Cl. sporogenes* both wounds	Yes	Yes	Recovery	
Amputation. 48 hr. later, excision of adductor muscles	457,000 units bivalent	10,000 units three times	20,000 units every 3 hr.	1,060,000 units	Yes	Yes	Clostridium (*Welchii* ?). Gram-negative bacilli. Gram-positive coccus	Not done	Yes	Recovery	
Amputation mid-thigh, left. Amputation, lower leg, right	None	20,000 units twice	20,000 units every 3 hr.	1,000,000 units	—	Not done	Clostridia from both wounds	Yes	Yes	Recovery	
Amputation	300,000 units polyvalent	100,000 units once 50,000 units once	20,000 units every 2 hr.	1,100,000 units	—	Yes	*Cl. welchii*. Hæmolytic streptococcus. Hæmolytic *Staphylococcus aureus*	Not done	Yes	Death	Local infection controlled. Death due to uræmia. Kidneys showed hæmoglobinuric nephrosis

in crash landings. In a single hospital where studies on wounds received in aerial combat have been made, the incidence of clostridial infection (recognizable clinical gas gangrene) has been 1·8 per cent.

The débrided tissue from 110 aerial warfare wounds was cultured anaerobically and clostridia were present in 27 wounds (24 per cent). Of the 27 cases only 3 developed gas gangrene. Thus the incidence of clostridial contamination in aerial warfare wounds is to be compared with that published for battle casualties in the present conflict (20–30 per cent) (MacLennan, 1943) and with the highest figure for accidental civilian wounds (39 per cent) (Altemeier and Gibbs, 1944). Soil, so frequently the source of such contamination in land fighting, is obviously not a direct factor in the aeroplane. It is known that clostridia can be grown from the skin (Roberts, Johnson, and Bruckner, 1937) of normal individuals as well as from wool (Schenken, quoted by Maes, 1940). Therefore, two potential direct sources of clostridial contamination remain—the airman's own skin, and his woollen clothing. Scarcely a single penetrating or perforating wound of aerial combat is free from small particles of flying suit, many of them embedded in deep recesses of the wound and lying in intimate contact with traumatized tissues. With these data at hand, it is difficult for us to understand why clostridial infections have not been reported from the flying personnel of our allies or from our own Air Forces in other theatres of war.

In commenting on the widespread distribution of the clostridia, MacLennan (1943) points out that " their absence from war wounds is a

matter of surprise rather than satisfaction, their presence for resignation rather than alarm". Moreover, the universal presence of clostridia is emphasized by the finding of clostridia in cranial wounds though clinical gas gangrene is not present. This finding of ours is substantiated by the reports from the Russian neurosurgeon, Propper-Graschenkov, who told the Surgical Mission whilst on its visit to his clinic in July, 1943, that he had recovered clostridia from 12·4 per cent of cranial wounds although he had never seen a case of "foamy brain", the clinical finding in established intracranial clostridial infections.

All of this suggests that something other than the presence of the organism is the determining factor. The universally recognized relation of reduction in circulation, with its resultant anoxia, and the generally accepted surgical finding that the incidence of and mortality from gas gangrene decreases as débridement improves and devitalized tissues are completely removed, certainly emphasizes the role of relative anoxia, and leads us back to adequate surgery as the chief therapy in the reduction of gas gangrene in the wounded of our armies.

SUMMARY

1. Seven cases of gas gangrene treated with local and parenteral penicillin are reported.

2. Five of these cases received penicillin immediately following primary débridement. In spite of prophylactic administration of penicillin, gas gangrene developed. However, after receiving surgical extirpation of the diseased tissue, gas-gangrene antitoxin, and continued penicillin therapy, each one recovered.

3. Two patients did not receive penicillin prophylactically but did receive it therapeutically. One of these died in uræmia five days following amputation. The kidneys showed hæmoglobinuric nephrosis.

4. Observations at one hospital place the incidence of clostridial contamination in wounds of aerial warfare at 24 per cent, the incidence of gas gangrene complicating wounds of aerial combat at 1·8 per cent.

CONCLUSIONS

Penicillin used prophylactically locally and parenterally in wounded and injured flying personnel did not prevent the development of gas gangrene. The role of this agent in modifying or altering the infection or influencing a favourable outcome cannot be evaluated on the basis of the small evidence at hand. Our data indicate proper surgical débridement is the major factor in both the prophylaxis and therapy of gas gangrene.

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INTRAPLEURAL PENICILLIN IN PENETRATING WOUNDS OF THE CHEST*

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WHILE it is generally admitted that penicillin is invaluable in wounds of the chest wall, its place in the treatment of hæmothorax is not so certain.

This paper deals with a series of penetrating chest wounds under our care at a Chest Centre with an Advanced Base Hospital. The patients have reached us usually within two days of injury, being sent to us direct from a Casualty Clearing Station. In a previous series treated under similar conditions in Tripolitania, Nicholson and Scadding reported (*Lancet*, 1944, March 4) an empyema rate of 33 per cent in hæmothoraces. In their series there was a high proportion of staphylococcal infections. Sulphathiazole was given orally, the hæmothorax being aspirated or evacuated by a thoracotomy in the clotted cases. In the present series sulphathiazole has been given orally, and the hæmothorax aspirated. At each aspiration penicillin has been injected into the pleural cavity. At first it was reserved for those cases in which an organism was recovered from the initial aspiration. It had been our experience that in fluid hæmothoraces if infection occurred organisms were usually to be found at this stage; this is not the case in clotted or multilocular hæmothoraces. The immediate results of intrapleural penicillin therapy were not encouraging in the infected cases. With larger supplies it was then possible to extend its use to all hæmothorax cases, replacing it after each aspiration as a prophylactic against infection. Only a small series of cases has been so treated and observed long enough to compare with the previous series of cases from North Africa. Evacuation must necessarily rob the clinician of knowledge of the

* Submitted by a surgical team for chest surgery, C.M.F.

final results in many cases; for this reason several patients treated with penicillin have not been included in this series. Moreover, because infected cases are held at a Chest Centre till fit to travel, there will always be an abnormally high incidence of sepsis in any figures from such a Centre.

Finally, during the last six months a much more radical operation has been performed in clotted and loculated hæmothoraces; not only has the clot been evacuated, but nearly always the lung has been completely re-expanded after decortication. Penicillin has been given in all these cases, and combined with operation has yielded very satisfactory results.

With due regard to the above statements, it is still possible to analyse the results obtained in the three groups of patients so treated, the fluid hæmothorax, the clotted hæmothorax, and the simple uncomplicated retained foreign body.

FLUID HÆMOTHORAX

After each aspiration we have replaced 30,000 units of sodium penicillin in 50 c.c. of normal saline, the aspirations and replacements being repeated every two or three days till the pleural cavity is dry. Occasionally the dose has been doubled in infected cases. In a few instances severe pain was felt in the affected side accompanied by pallor, restlessness, and an increase in both the pulse and respiration rates. The pain has been intense enough to require morphia, but has never lasted more than half an hour. We have not observed any clotting of the hæmothorax due to penicillin. No other sign of pleural irritation such as increased effusion has been noted, nor does it appear that Gram-negative organisms have ever been introduced with the penicillin. Altogether 42 cases have been treated and observed long enough to be analysed, the group comprising patients wounded in January, February, and March of this year. At first the scarcity of the drug made it necessary to reserve it for infected cases, so that it was not given till after receipt of a bacteriological report on the pleural fluid; thus, a delay of three or four days in instituting treatment was common in the early cases, but as more supplies became available it was given at the initial aspiration in every case. It must be appreciated that the fluid hæmothoraces are a selected group, not including patients so frankly infected on arrival at the Chest Centre that immediate intercostal drainage was instituted, or clotted hæmothoraces in which infection is more common. The group therefore consists of those cases which should do well with simple aspiration. Of the 42 hæmothoraces, 27 remained sterile throughout; 15 were infected, and of these only two settled without drainage. The empyema rate (31 per cent) in this group is no less than our average figure for the last two years, but it is undoubtedly exaggerated by the selection of infected cases for penicillin therapy in January; this is somewhat balanced by the elimination of the clotted and grossly infected cases already requiring drainage. The significant fact is that once pathogenic organisms are present in the pleural fluid it is unusual for drainage to be avoided. As will be seen in *Table I*, Gram-positive organisms were responsible for the majority of cases which came to rib resection, only one case requiring drainage for Gram-negative organisms. This does not imply that the organism always continued to grow, for in some cases sterile pus required drainage.

Table I.—ORGANISMS IN INFECTED HÆMOTHORACES WHICH REQUIRED RIB RESECTION

	GRAM-POSITIVE	GRAM-NEGATIVE	MIXED
Fluid hæmothoraces	10	1	2
Clotted hæmothoraces	4	1	5

Case Reports.—

Case 1.—Pte. H. Penetrating shell wound with a small retained splinter in the right lower lobe; right hæmothorax. Aspirated three times at Casualty Clearing Station, with removal of 1 pint of blood each time, before admission to the Chest Centre on the tenth day.

10*th day*. Aspiration yielded blood without excess of polymorphs, growing *Staph. aureus* on culture.

12*th day*. Aspiration and replacement of 30,000 units of penicillin.

Smear: No excess of polymorphs. Gram-positive cocci.

Culture: *Staph. aureus*, and non-hæmolytic streptococcus on anaerobic culture.

14*th day*. Aspiration of bloodstained effusion. Replacement with 30,000 units of penicillin.

Smear: Pus cells and Gram-positive cocci.

Culture: *Staph. aureus*.

16*th day*. General condition much improved. Aspiration of thin turbid effusion. Replacement with 30,000 units of penicillin.

Smear: Pus cells; no organisms seen.

Culture: Light growth of *Staph. aureus*.

20*th day*. Aspiration of chocolate pus. Replacement with 60,000 units of penicillin.

Smear: Pus cells and Gram-positive cocci.

Culture: *Staph. aureus*.

24*th day*. Rib resection for a residual basal empyema.

Comment.—Failure to sterilize a small infected hæmothorax. Therapy was instituted rather late.

Case 2.—Capt. H. Perforating shell wound of the lower lobe, right, with a total right hæmopneumothorax; atelectasis of the right lung, with no retained foreign body.

2*nd day*. Initial aspiration at Casualty Clearing Station.

4*th day*. Aspiration at Chest Centre.

Smear: No organisms; no excess of polymorphs.

Culture: Sterile.

8*th day*. Aspiration of an anterior loculus.

Smear: No excess of polymorphs. A few cocci.

Culture: Light growth of *Staph. aureus*.

10*th day*. Aspiration and replacement with 30,000 units of penicillin.

Smear: No excess of polymorphs. Cocci.

Culture: Heavy growth of *Staph. aureus*.

12*th day*. Aspiration and replacement with 30,000 units of penicillin.
Smear : No excess of polymorphs. Cocci.
Culture : Light growth of *Staph. aureus*.
14*th day*. Aspiration and replacement with 30,000 units of penicillin.
Smear : An occasional polymorph. No organisms.
Culture : Sterile.
By this time the lung was completely atelectatic and fluid was forming quickly, the aspirations being of about a litre each time.
16*th day*. Aspiration and replacement with 30,000 units of penicillin.
Smear : No excess of polymorphs. No organisms.
Culture : Sterile.
21*st day*. Aspiration and replacement with 30,000 units of penicillin.
Smear : No excess of polymorphs. Coliforms.
Culture : *B. proteus*.
24*th day*. Aspiration of thick yellow turbid fluid, like yolk of an egg.
Smear : No excess of polymorphs. No organisms.
Culture : Pure growth of *B. pyocyaneus*.
27*th day*.—OPERATION. Thoracotomy, evacuation of macroscopic pus and debris and repair of a small bronchial fistula in the lower lobe. A decortication was not performed in this instance, but now in a similar case it would be done. Drainage of a total pyothorax, from which the *B. pyocyaneus* was cultured.
Comment.—Effective removal of staphylococcus, but nevertheless an empyema required drainage. The fistula was, and must frequently be, a complication. The correct treatment here would have been to do a decortication as soon as the staphylococcus was eliminated, since the lung showed no sign of expansion; subsequently it expanded slowly with suction drainage.

Conclusion.—Intrapleural penicillin is not usually effective in eliminating infection in a hæmothorax; the series is too small to judge how effective it may be in preventing infection when given early.

CLOTTED OR MULTILOCULAR HÆMOTHORAX

During the last three years we have found that radical evacuation of clotted or loculated hæmothoraces by thoracotomy gives the best results. More recently a decortication has been performed in the majority of clotted cases. The re-expansion of the lung so effected must play a major part in preventing a late empyema developing. Penicillin has been used in these cases, the advent of the drug coinciding with a more radical surgical policy. It is, therefore, difficult to assess how much each contributes to the general success in these cases; but we have the impression that penicillin may be making these patients safe for surgery. The cases so treated fell into three groups :—

1. It has been possible to sterilize the pleural cavity before operation, in some of the multilocular cases, but sometimes it is found that the drug does not penetrate one loculus or a fibrin clot, which continues to harbour organisms.

Case Report.—
Case 3.—Gdsm. H. Perforating gunshot wound of the left lower lobe with an infected hæmothorax.
1*st day*. Aspiration of blood at Casualty Clearing Station.
2*nd day*. Aspiration of blood at Casualty Clearing Station.
12*th day*. Arrival at Chest Centre. Aspiration of infected bloodstained fluid.
Smear : Pus cells and Gram-positive bacilli.
Culture : *Cl. welchii*.
14*th day*. Aspiration and replacement with 60,000 units of penicillin.
Smear : Pus cells and Gram-positive cocci.
Culture : *Cl. welchii*.
16*th day*. Aspiration and replacement with 30,000 units of penicillin.
Smear : Pus cells. No organisms.
Culture : Sterile.
18*th day*. Aspiration of thin pus and replacement with 60,000 units of penicillin.
Smear : Pus cells. No organisms.
Culture : Sterile.
20*th day*. Aspiration of thicker pus.
Smear : Pus cells. No organisms.
Culture : Sterile.
24*th day*. Aspiration of thick pus.
Smear : Pus cells. No organisms.
Culture : Sterile.
27*th day*. Thoracotomy, evacuation of massive clots and fibrin, and decortication. The lung expanded immediately, leaving only a small basal empyema, which was drained.
Comment.—This patient had massive clots which could not have been removed without thoracotomy; in this instance the penicillin did sterilize the clot, which was cultured; by sterilizing the pleural cavity it reduced the risk of re-infection at operation. His convalescence was remarkably smooth.

2. After evacuation of clot and decortication, 30,000 units of penicillin is left in the pleural cavity to deal with any organisms present. All cases have been drained with an intercostal tube for 2 to 3 days, so that a compromise has been reached by clipping off the drainage tube during the first twelve hours after operation. During this period the penicillin is most active in the pleural cavity. After twelve hours the clip is released, and the pleural cavity drains. In the majority of patients the tube is removed on the second or third day, a further 30,000 units of penicillin being injected down it immediately before its removal.

Case Report.—
Case 4.—Lieut. G. Perforating gunshot wound of the left lower lobe, with a clotted hæmothorax.
Pre-operative aspiration (small).
Smear : Pus cells and cocci.
Culture : *Staph. aureus*.
Thoracotomy, evacuation of clot, and decortication of both lobes. Complete expansion. Intrapleural penicillin and intercostal drainage, the tube being clipped off for the first 12 hours.
On the third post-operative day a specimen of fluid was taken from the drain :—
Smear : No pus cells.
Culture : Coliforms only.
30,000 units of penicillin were injected down the tube, which was again clipped for 12 hours.
On the fifth post-operative day a further sample was collected, which again grew coliforms, pus being absent. As the drainage was very small, the tube was removed.

The patient made a rapid recovery, the lung being completely expanded. He was afebrile, up, and had a clear radiograph at the end of three weeks.

Comment.—This is the type of case in which we find penicillin of most value; maybe such cases would settle without chemotherapy, but it is reasonable to suppose that there is less risk of residual infection if penicillin is employed.

3. A small residual empyema after thoracotomy for clot may sometimes settle with penicillin instillations, provided it can be completely emptied at each aspiration. Even so, caution must be exercised in assessing cure in these cases; a chronic empyema may lie dormant in an apparently healed cavity. We have sterilized two or three such residual pockets, but although the patients were in excellent health it is not claimed that they were finally cured without drainage, as in each case it was necessary to evacuate them before they had been adequately observed.

Conclusion.—As will be seen from *Table II*, a large number of cases infected with Gram-positive organisms did settle without rib resection after thoracotomy, decortication, and intrapleural penicillin. Altogether, in 42 thoracotomies for clotted or loculated hæmothoraces, 18 were uninfected throughout, 14 were infected but settled without forming empyemata, and 10 formed empyemata. The empyemata rate is therefore lower (24 per cent) than in the fluid hæmothoraces.

Table II.—Organisms in Infected Hæmothoraces which Settled

	Gram-positive	Gram-negative	Mixed
Fluid hæmothoraces	2	Nil	Nil
Clotted hæmothoraces	12	2	Nil

We believe that penicillin has been of value in these cases in reducing the virulence of the infection and enabling adequate surgery to be safely undertaken.

FOREIGN BODIES

In twelve consecutive operations for removal of foreign bodies from the lung or pleural cavity, unassociated with an infected hæmothorax, penicillin was used locally in the pleural cavity, 30,000 units in each case. *Table III* shows that although 10 of the foreign bodies grew organisms on culture, yet no instance of infection arose.

Table III.—Results in the Presence of Infected Foreign Bodies

Case No.	Foreign Body	Result
1	Sterile	No infection
2	Gram-positive	No infection
3	Gram-positive and Gram-negative	No infection
4	Gram-positive	No infection
5	Gram-positive	No infection
6	Gram-positive	No infection
7	Gram-positive	No infection
8	Gram-positive	No infection
9	Sterile	No infection
10	Gram-positive	No infection
11	Gram-positive	No infection
12	Gram-positive	No infection

SUMMARY

1. At the dosage employed, penicillin injected into the pleural cavity usually failed to prevent the formation of an empyema in infected hæmothoraces.

2. Many infected clotted hæmothoraces have settled without forming empyemata after adequate surgery and local penicillin.

3. Penicillin was used locally in a series of operations for foreign bodies without subsequent infection.

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PENICILLIN IN THE TREATMENT OF WAR WOUNDS OF THE CHEST*

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INTRODUCTION

The patients in this series were injured in Italy. Surgeons who had worked in the Western Desert and North Africa and who are now in Italy agree that infection is more common and more formidable in this theatre. This increased incidence is sepsis should be appreciated so that the good results of the conservative treatment of chest wounds in Africa should not induce an unduly optimistic frame of mind. Under modern battle

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conditions major thoracic surgery is rarely practised in the Forward Areas; there, the chief aims have been to save life by resuscitation, to close by various methods the open sucking pneumothorax wound, and to aspirate air and hæmothorax fluid. The patients at this centre have arrived 3 to 30 days after being wounded. This must be remembered when the following figures, which give an indication of the infection problem, are considered :—

Number of serious consecutive chest wounds	202
Number of empyemata (pyopneumothorax and pyothorax)	66

Since most of these patients reached this centre already infected, it is felt that the prevention of this high infection rate should be attempted by adequate aspiration, combined with penicillin treatment, in the Forward Areas. Such a combination requires specialized management by a forward thoracic unit working in conjunction with a unit at the Base, as in the case of neurosurgical and maxillofacial units. This is not intended as a criticism of the present forward units, but assumes that such a team, with specialized equipment and experience, would be able to concentrate on the difficult technique of intrapleural penicillin treatment. Haphazard penicillin therapy for chest wounds is extravagant and ineffective.

Out of these 202 serious war wounds of the chest, 64 lesions have received penicillin treatment. These are classified as below. It will be noted that in 58 instances the treatment has been for established infection :—

SECTION I.—**In the Treatment of Established Pleural Infections (Infected Hæmothorax, Empyema, Pyopneumothorax).**

Group A. Parenteral sodium penicillin	11	6 failures to stop Gram-positive pyogenic bacterial growth
Group B. Local intrapleural injection following aspiration	14	1 failure to stop pyogenic bacterial growth
Group C. Parenteral and intrapleural injection following aspiration	3	0 failures

SECTION II.—**Prophylactic Use.**

Group A. Course of parenteral sodium penicillin after major thoracotomy—no drainage	3	1 failure to remove Gram-positive pyogens from the pleural cavity
Group B. Instillations—intrapleural after thoracotomy without drainage	5	0 failures
Group C. Insufflation into wounds of lung tissue followed by suture and chest wall closure without drainage	4	0 failures

SECTION III.—**Local Calcium Penicillin Treatment (for Severe Chest Wall Wounds, and certain Lesions Deep to the Rib Plane—Extrapleural Hæmothorax, Lung Abscess, etc.).**

Group A. Calcium penicillin instillation and complete wound suture	7	0 failures to obtain complete union*
Group B. Repeated insufflation of penicillin-sulphathiazole powder followed by suture	3	0 failures
Group C. One application of penicillin-sulphathiazole powder and immediate suture (only used for mildly infected wounds)	7	0 failures
Group D. For localized intra-thoracic lesions: extrapleural hæmothorax; lung abscess; localized intrapleural effusions	3	0 failures

SECTION IV.—**Parenteral Sodium Penicillin associated with Closure by Suture of very serious Septic Chest Wall Wounds.**

Cases treated	4	1 failure; union was 60 per cent successful in this "failure"
TOTAL CASES TREATED	64	9 failures to prevent pyogenic bacterial growth or secure complete union of wounds

* Three sutured wounds broke down after closure by instillation technique using a "merthiolate penicillin" solution. Subsequently the manufacturers reported that this solution contained no active penicillin.

SECTION I.—PENICILLIN IN THE TREATMENT OF ESTABLISHED PLEURAL INFECTIONS

Apart from a few cases where a pneumothorax cavity became infected, infection had developed in an incompletely aspirated hæmothorax. Clinical recognition of infection often precedes bacteriological proof, since the organisms may at first be shut off in a loculus in the pleural cavity, or in the fibrinous clots which are frequently seen (*see Fig.* 100), and thus do not appear in the specimen of aspirated fluid sent for examination. We have taken the following criteria as evidence of infection, and two at least have been present in all the cases in this series.

1. *Significant Pyrexia.*—A nightly rise of temperature to 99°–100° is the rule in the uninfected hæmothorax in the first ten days and may continue into the third week. Higher temperatures, which are temporarily reduced by aspiration, but recur afterwards, usually with fresh fluid formation, are highly suggestive of pleural infection.

2. *Appearance of Microscopic and Macroscopic Pus.*—In the early stages of infection an increase of pus cells is seen in the smear from the aspirated fluid, and this stage is quickly followed by a change in colour of the effusion from clear red to turbid pink until frank pus is present. Even at this stage, organisms may not be found on culture of the fluid, but at thoracotomy they have usually been recovered from the intrapleural fibrin.

3. *Presence of Pathogenic Organisms on Direct Examination of Pleural Fluid or Fibrin, or on Culture.*—Previous experience would have led us to drain all the cases under consideration.

The methods used in the treatment of these cases before penicillin was available have been the conventional ones of aspiration followed by closed intercostal drainage, rib resection, and closed Tudor Edwards's drainage (sometimes combined with thoracotomy and clearance of infected clot from the pleural cavity), and, finally, open drainage. The results have been moderately satisfactory, although in a series of 40 cases there were 6 deaths; but when compared with the empyemata of civilian practice toxæmia and pyrexia have been prolonged, even when adequate drainage has been established, 'pocketing' of the empyema cavity has been common, and the wound sepsis and bronchopleural fistula which are frequently present often lead to a recrudescence of pyrexia from reinfection of the cavity with virulent organisms. In only two of the 40 cases had complete healing (i.e., complete chest wall healing and lung re-expansion) taken place in two months, and the average period of healing was nearer six months.

Once the technique of intrapleural injection of penicillin following aspiration was found to be the best method of treatment, the following comparative results were obtained.

It will be seen that the use of penicillin reduces both the mortality and the period of invalidism. The objects of any form of treatment can be summarized as follows:—

a. To control Gram-positive infection in the wall of the pyothorax cavity and the contents of the cavity.

No. of Cases	No. Drained	Deaths	No. Healed Clinically and Radiologically within 2 Months
Non-penicillin treated, 40	40	6	2
Penicillin treated, 12	2	0	12

b. To secure early apposition of the walls of the cavity with a minimum of pleural thickening, both with a view to rapid restoration of function and because of the possibility of reinfection of the sterilized cavity.

Penicillin can solve the first problem, but mechanical measures may still be necessary to deal with the mechanical problem. Our first cases were treated with general parenteral penicillin by the intramuscular or intravenous route. and in a few cases this was combined with simultaneous intrapleural instillation, but all our later cases were treated with intrapleural penicillin only. The results in these three groups will be considered separately.

Group A. General Penicillin Only.—Sodium penicillin was given by intramuscular injection of 15,000 units 3-hourly for 2 days and 4-hourly for 3-8 days. In some cases it was found more convenient to give 120,000 units per day in a glucose saline intravenous drip for all or part of the period of treatment. The cases fall into two classes: (1) Without simultaneous drainage; (2) With simultaneous drainage.

1. In the first of these groups (*Table I*), of 8 cases, complete and permanent destruction of Gram-positive organisms of the pleural cavity was only obtained in 2 cases. In some of the others significant reduction in the number of organisms and in toxæmia was obtained, but the subsequent course of the illness was not greatly affected. Pleural fluids from several of these cases were examined for penicillin, and significant amounts were never found. Our results with intrapleural penicillin suggest that the drug passes but slowly through the pleura, and it is clear that while general penicillin may influence the infection in the wall of the cavity it will seldom sterilize the contents of an infected hæmothorax. Further trial of this method seems undesirable.

2. In the second of these groups (*Table II*) in 3 cases the pleural discharge was rapidly sterilized, but in the first 2 patients (*Cases* 9 and 10) sterilization of the cavity could have been more easily achieved by intrapleural instillations. *Case* 11

arrived severely ill with the clinical signs of septicæmia and with a total empyema draining imperfectly through an intercostal catheter; his condition was too bad for immediate rib resection, but was greatly improved with a normal temperature after 3 days' general penicillin, and rib resection was then carried out. The size of the cavity would have made local application very difficult, and a place for the use of general penicillin may exist in this type of case.

treated by intrapleural penicillin. It will be seen from *Table III* that, with one exception, destruction of Gram-positive pyococci in the cavity was successfully achieved.

The cases fall into two groups: (1) Intrapleural penicillin without or before drainage; (2) Intrapleural penicillin after drainage.

1. In the first group as much fluid and air as possible was aspirated from the cavity and sodium penicillin injected at the end of the aspiration

Table I.—SECTION I, GROUP *A*. GENERAL PENICILLIN ONLY: (1) WITHOUT SIMULTANEOUS DRAINAGE (8 *Cases*)

CASE NO.	CONDITION AT COMMENCEMENT OF TREATMENT			CONDITION AT END OF PENICILLIN COURSE			SUCCESS– OR FAILURE*	FINAL RESULT
	Bacteriology	Size of Empyema	Toxæmia	Bacteriology	Size of Empyema	Toxæmia		
1	Pneumococci ++ *Staph. aureus* + Clostridia +	+++	+++	Pneumococci +, Clostridia +	+++	+	F.	Intercostal drainage and and rib resection. Slow re-expansion
2	*Staph. aureus* +	++	++	Sterile	+	o	S.	Thoracotomy and clot clearance without drainage. Complete healing within month of the operation
3	Pneumococci +++	++	++	Pneumococci ++	++	+	F.	Empyema later sterilized with intrapleural penicillin
4	*Staph aureus* ++ Hæm. Streps. + Clostridia +	+++	+++	*Staph. aureus* +++ Hæm. Streps. + Clostridia ++	+++	++	F.	Intercostal drainage and rib resection. Slow re-expansion of lung
5	*Staph. aureus* +, *H. influenzæ* +, Clostridia +	++	++	*H. influenzæ* + (penicillin-resistant), Clostridia +	+	o	S.	Thoracotomy and clot clearance without drain followed by intrapleural penicillin and succinyl sulphathiazole. Healing apart from small cavity containing 2 oz. sterile serous fluid in 6 weeks from operation
6	*Staph. aureus* ++	++	+	*Staph. aureus* +++	+	+	F.	Later sterilized with intrapleural penicillin
7	Pneumococci ++, (penicillin-resistant)	++	++	Pneumococci ++	++	++	F.	Intercostal drainage and rib resection. Slow re-expansion
8	*Staph. aureus* +++ (penicillin-resistant)	++	++	*Staph. aureus* ++ Hæm. Streps. +	++	++	F.	Intercostal drainage. Rib resection. Slow re-expansion

* Success = Removal of Gram-positive pyogens. Failure = Failure to remove Gram-positive pyogens.

Table II.—SECTION I, GROUP *A*. GENERAL PENICILLIN ONLY: (2) WITH SIMULTANEOUS DRAINAGE (3 *Cases*)

CASE NO.	CONDITION AT COMMENCEMENT OF TREATMENT		CONDITION AT END OF PENICILLIN COURSE		SUCCESS OR FAILURE	FINAL RESULT
	Bacteriology	Toxæmia	Bacteriology	Toxæmia		
9	*Staph. aureus* +++, Clostridia +	+++	*B. proteus*, Diphtheroids, *Staph. albus*	±	S.	Rapid re-expansion of lung in six weeks. Almost apyrexial course
10	Hæm. Streps. +++	++	*B. pyocyaneus*, *B. coli*	±	S.	Rapid re-expansion of lung. Cavity later re-infected and a pocket became shut off, requiring local instillations.
11	*Staph. aureus* ++	+++	Diphtheroids, *B. proteus*	±	S.	A total empyema which is expanding very slowly and has become re-infected since

Group B. Intrapleural Penicillin Only.—Twelve cases (*Table III*) were treated by intrapleural injections of penicillin following aspiration. Two cases already drained were through the aspirating needle. The usual dosage employed was 60,000 units in 60 c.c. warm normal saline, and it was usual to find from 1–5 units per c.c. in fluid aspirated 48 hours after and

sometimes as much as 4 days later. In some of the larger cavities, however, no penicillin was found after 48 hours, and in some of the smaller ones 30,000 units was sufficient to maintain a high concentration for this period. The concentration of 1–5 units per c.c. is considerably higher than that attained in the blood ($\frac{1}{10}$ unit per c.c.) with the usual dose of parenteral penicillin, but it has the great advantage of producing rapid sterilization and should inhibit the growth of most 'resistant' pneumococci, though it is doubtful if it will control all strains of staphylococci. It will be seen that in the majority of cases one instillation was sufficient to sterilize

Table III.—Section I, Group *B*. Intrapleural Penicillin only: (1) Without, or Before, Drainage. Given through Aspirating Needle

(12 *Cases*)

Case No.	Condition before Treatment			Condition after Course of Penicillin			Success or Failure. No. of Injections. Total Dosage before Sterilized	Final Result (F.U. — Follow Up)
	Bacteriology	Size of Cavity	Toxæmia	Bacteriology	Size of Cavity	Toxæmia		
12	Gram-positive cocci, not cultured	++	++	Sterile	+	o	S.	8 weeks after commencement of treatment, a very small cavity containing no fluid remains. No drainage. F.U., 12 weeks, no cavity left
13	*Staph. aureus* ++	+++	+++	Sterile	+	+	S. One injection 60,000 units	Residual effusion became heavily infected with *B. pyocyaneus* and a small cavity was drained
14	*Staph. aureus* +++ (Appears also in *Group A* as *Case* 6)	+	+	Sterile	o	o	S. Three injections 90,000 units	Up, afebrile, and cavity closed 2 weeks after first injection, No drainage. F.U., 2 months, completely well
15	Hæm. Streps. ++, *Staph. aureus* +, *B. proteus*	++	+	*B. coli* +, *B. pyocyaneus*	+	o	S. One injection 60,000 units	Developed massive collapse after thoracotomy, was a candidate for total empyema. Complete re-expansion after 2 months. No drainage
16	Pneumococci ++, *B. coli* ++	+	++	*B. coli*, *B. pyocyaneus*	+	o	S. One injection 60,000 units	Patient had a broncho-pleural fistula. 6 weeks after start of treatment a small dry cavity size of a walnut remained. No drainage. F.U., 2 months, no cavity
17	Hæm. Streps, +++ *B. pyocyaneus* +	+++	+	*B. proteus*, *B. coli*, *B. pyocyaneus*	++	o	S. Two instillations 120,000 units	Cavity more than half reduced in size in 2 weeks. Heavy *B. coli* infection necessitated drainage. Rapid re-expansion
18	*Staph. aureus* +++	++	++	This patient's fluid was sterile after 1 instillation of 60,000 units sodium-penicillin, but one month after operation his temperature rose again and the pleural cavity was explored. One half ounce thick pus containing *Staph. aureus* +++ was found. The cavity was lost before penicillin could be instilled. One month later there was no recurrence. Classified as a bacteriological failure, but 3 months later completely healed clinically and radiologically.				
19	Pneumococci +++	++	+	Sterile	+	o	S. One injection 60,000 units	Clot clearance by minor thoracotomy. No drainage. Up, afebrile, lung re-expanded 10 days after operation. 3 weeks after first instillation. F.U., 2 months, no recurrence
20	*Staph. aureus* +++	++	++	Sterile	+	o	S. Four injections 150,000 units	Up and afebrile with small dry cavity 1 month after first instillation. No drainage. F.U., 2 months, no cavity
21	Non-hæm. Streps++	++	++	Sterile	+	o	S. One injection 60,000 units	Three weeks later lung almost re-expanded. Cavity dry. No drainage. F.U., 2 months, no cavity
22	Streptococci ++++ in fibrin (overgrown by *B. coli* on culture)	+	+++	Fluid did not re-accumulate	o	o	S. One injection 30,000 units	Cavity rapidly closed without drainage.
23	*Staph. aureus* +++	++	++	Sterile	+	o	S. Two injections 120,000 units	Four weeks after first aspiration small dry cavity remains. Up, afebrile. No drainage.
	(2) After Drainage. Given through Intercostal Catheter. (2 *Cases*)							
24	Hæm. Streps. +++ Clostridia	++	++	*B. coli*, *B. pyocyaneus*	+	o	S.	Rapid expansion of lung with intercostal drainage only. Closure of cavity in 2 months
25	Hæm. Streps. +++ *Staph. aureus* +, (Appears also in *Group A* as *Case* 7)	++	++	*B. proteus*	+	o	S.	A further re-infection of the cavity occurred at a later date but was again controlled by instillations of penicillin. Gradual re-expansion has continued. 2 months later—well, and no cavity

the cavity in 24–48 hours, i.e., the next aspiration, and in none of the successful cases were more than three instillations necessary.

The fluid aspirated from penicillin-treated cavities usually remains purulent, even in the absence of Gram-negative infection, for 2–3 weeks, and then gradually becomes serous. Clinical improvement is usually dramatic; it is rare for pyrexia to persist after the second injection, and most patients have been up in the ward within 10 days of their first treatment.

Our experience suggests that 60,000 units of penicillin is the correct dose for average cavities holding from 10 to 20 oz. of fluid, and that 120,000 units should be given for total empyema and 30,000 units for small pockets. Three to four aspirations and instillations at 48-hour intervals should suffice as a routine, but bacteriological control is obviously desirable. It has been our custom to posture patients who have much air in the pleural cavities for 3 hours on each side, so as to distribute the penicillin widely. It is clear that this method is more efficient and more convenient than the use of intravenous or intramuscular penicillin.

2. In the second group 2 cases were treated by injecting 60,000 units of penicillin in 4 oz. of saline into the drainage tube. The tube and wound were carefully blocked off by spigot and packing and the patient was placed on the opposite side for 3–6 hours. After 24 hours closed drainage was reinstituted and penicillin treatment repeated. In both cases sterilization was rapidly achieved, though in one case reinfection along the tube track took place at a later date.

DISCUSSION

We have seen that in the great majority of cases infected hæmothorax and empyema can be rapidly freed from Gram-positive organisms by intrapleural penicillin alone, and that a similar result can be achieved in empyemata already draining by intrapleural penicillin, combined with general penicillin if the chest wall is infected or the patient severely ill.

In Section I, *Groups B* and *C*, 14 out of 15 cases lost their Gram-positive pyogens without or before drainage; 10 of these have healed without resorting to drainage. In 5 of them minor thoracotomy for clearance of massive fibrin clot, followed by aspiration, was undertaken, and in the other cases aspiration alone was used. Aspiration has usually been performed twice weekly for the first 2 weeks after sterilization, and then weekly; it requires good radiological control and an experienced operator if it is to be successful, since the localization of pockets is not always straightforward. These 10 patients were up and afebrile for the greater part of their treatment, and the cavity was obliterated or dry in a month or less in 6 cases and in 2 months in the rest.

Five cases were operated on, the indication being the same in all—heavy infection with Gram-negative organisms resulting in pyrexia and the continued production of pus which prevented further reduction in the size of the cavity. An effort to control the growth of these organisms by intrapleural injections of 2 per cent succinyl sulphathiazole suspension was made in some cases, and in 2 undrained cases the organisms disappeared afterwards, but the infection had never been heavy and the value of the method remains doubtful.

Table IV.—Section I, Group *C*. Simultaneous, General, and Intrapleural Penicillin (3 *Cases*)

Case No.	Condition at Beginning of Treatment			Condition after Treatment			Success or Failure	Final Result
	Bacteriology	Size of Cavity	Tox-æmia	Bacteriology	Size of Cavity	Tox-æmia		
26	Pneumococci +++	++	++	*B. pyocyaneus* +++	+	++	S.	Clearance of clotted hæmothorax. Drainage on account of heavy Gram-negative infection. Slow re-expansion
27	*Staph. aureus* +, *B. pyocyaneus* +	++	++	*B. pyocyaneus* +++	++	++	S.	Drainage on account of heavy Gram-negative infection. Slow re-expansion
28	Hæm. Streps. +++	+++	+++	*B. coli* +, *B. pyocyaneus* ++	+	+	S.	Drainage on account of heavy Gram-negative infection. Rapid re-expansion

Group C. Simultaneous General and Intrapleural Penicillin. Three cases were treated by this method.

It will be seen from *Table IV* that removal of the Gram-positive organisms from the cavity was rapidly achieved in all cases. Though in the light of later experience with *Group B* such a result would probably have been achieved with intrapleural penicillin alone, the general penicillin was of value in *Cases* 27 and 28, since it enabled septic chest-wall wounds to be sutured successfully.

Conclusions.—

1. Penicillin is a valuable aid to the treatment of infected hæmothorax and is best used by injections into the closed pleural cavity.

2. In those cases where, after 2 weeks' aspiration, there is evidence of much clot remaining,

minor thoracotomy through an intercostal space should be carried out, the clot evacuated, and the thorax closed. Aspiration should then be continued.

3. When infection by Gram-negative organisms leads to pyrexia and pus formation which is incompletely controlled by aspiration, drainage by intercostal catheter or rib resection should be instituted.

4. Reinfection with Gram-positive pyogens of the draining empyema cavity can be controlled by intrapleural penicillin through the drainage tube.

5. In severe toxæmia or chest-wall infection, general, as well as intrapleural, administration of penicillin is advised.

CASE REPORTS

In view of the limitation of space, case-histories of only a few patients can be given, and the following typical ones are appended. A short summary of the others is given in the tables.

Case 2.—Section I, *Group A*. **Shell wound, chest; mediastinal abscess; right infected hæmothorax.**

Dec. 9, 1943. Wounded by aerial bomb. Large sucking wound to left of upper part of sternum excised at F.S.U. The track led across the sternum to end in right chest. Right hæmothorax aspirated three times before admission to Chest Centre.

Dec. 24. *Admitted to Chest Centre.* Dyspnœic and toxic. Pus oozing from wound, especially on coughing or deep breathing. Right hæmothorax present. *Radiograph*: Right basal hæmopneumothorax, with effusion spreading into interlobar fissure. An irregular metallic F.B., 20 mm. × 8 mm. lying in an abscess cavity in the right paracardiac region. *Aspiration*: 4 oz. clear, serous fluid.

Dec. 29. General condition much deteriorated. Much pus from wound. *Aspiration*: 8 oz. orange-brown serosanguinous fluid. *Bacteriology*: *Str. pyogenes*. *Operation*: A probe in the upper wound led down from second left space to behind the fourth costal cartilage. The track lay superficial to the sternum. The cartilage was excised, and a large irregular F.B. lay in and was removed from a large abscess cavity to the right of the pericardium. This wound was left open after penicillin-sulphathiazole powder had been insufflated. *Bacteriology*: *Culture—Staph. aureus.*

Progress: In view of the infected hæmothorax a full course of sodium penicillin was started (15,000 units 3-hourly for 5 days).

Jan. 2, 1944. *Aspiration*: Right base—9 oz. fluid obtained. *Bacteriology*: *Film*—pus + + +, cocci +. *Culture—Staph. aureus* scanty.

Jan. 3. Sodium penicillin course stopped. Total dosage, 540,000 units.

Further Treatment: On the next aspiration (Jan. 5) the culture from the fluid was sterile, though many pus cells were still present. Three subsequent aspirations produced the same result.

Jan. 21. The general condition was excellent. He had been apyrexial for 3 weeks. Radiography showed a collection of fluid at the right base (*Fig.* 97). As the fluid was becoming difficult to aspirate, minor thoracotomy was decided upon to remove the clots and to encourage lung expansion. *Operation*: Through 7th right interspace the pleura was opened. It was not very thickened. The cavity contained 10 oz. of thick pus and some fibrin clots. Pleural toilet was done. The pleura around the lung was healthy in appearance and not thickened appreciably. The chest was closed completely without drainage.

Bacteriology of Fibrin: *Film*—pus + + +; no organisms seen. *Culture*—no growth. *Broth-culture*—coliforms +. *Sub-culture—B. pyocyaneus* + +, *B. coli* +.

Bacteriology of Pleural Fluid: *Film*—pus + + +; no organisms seen. *Culture*—no growth.

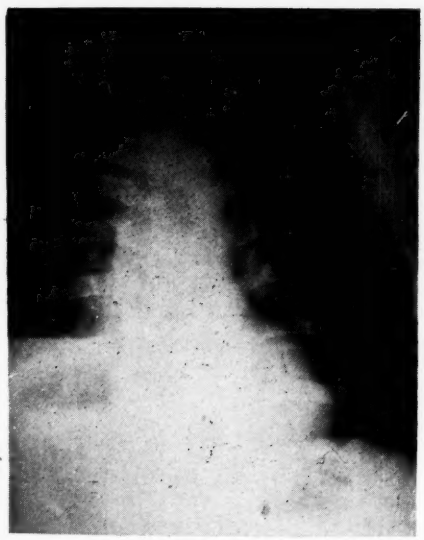


FIG. 97.—*Case* 2. Radiograph showing right effusion. This had contained pus and streptococci 10 days previously. At the time of this radiograph this effusion was sterile. It was evacuated by minor thoracotomy because of its content of fibrin.

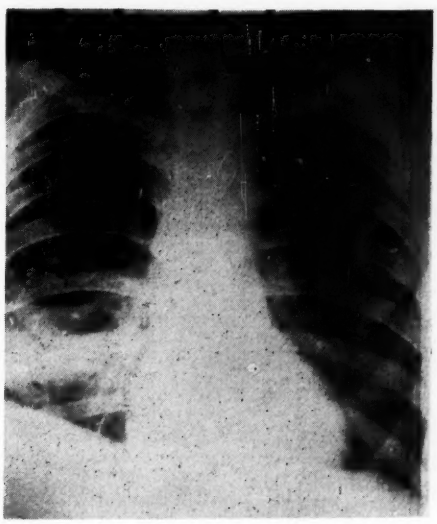


FIG. 98.—*Case* 2. Radiograph taken 25 days after thoracotomy for 'clot clearance'. Later radiographs showed complete resolution. Rib resection and drainage avoided successfully.

Progress: Excellent and uneventful. One post-operative aspiration was required (*Jan.* 27), when 4 oz. of fluid were withdrawn. Culture of this revealed no organisms. The wound healed by first intention

FIG. 99.—*Case* 2. First intention healing after the evacuation of an empyema infected by hæmolytic streptococci and treated by parenteral penicillin. The operation was done chiefly for the evacuation of fibrin clots. (*See text.*)

(*Fig.* 99), and the lung rapidly re-expanded. By *Feb.* 15 he was up and about the ward, well and apyrexial (*see Fig.* 98).

Comment.—Two months after wounding, this patient with a mediastinal abscess and an infected hæmothorax was well and ambulatory. The recovery time from operation and start of penicillin therapy was 7 weeks. The rapid sterilization of the infected pleural effusion is noteworthy.

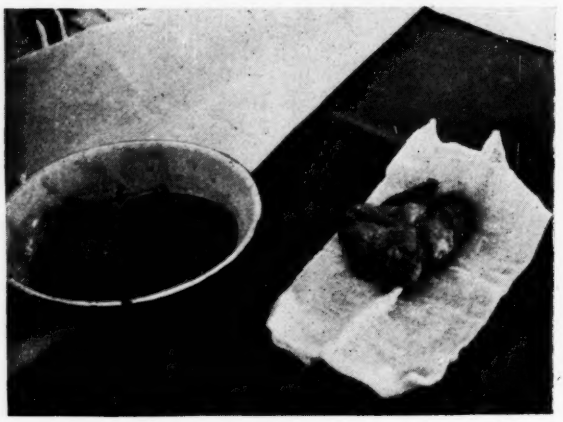


FIG. 100.—Photograph of fibrin clots removed by pleural toilet. This illustrates the importance of the treatment by surgery of the mechanical derangement that can be caused by fibrin formation in a hæmothorax.

Case 16.—Section I, *Group B.* **Gunshot wound (M.G.), tangential left thoraco-abdominal; left thoracotomy and laparotomy and splenectomy. Small left hæmothorax. Right empyema and bronchopleural fistula.**

Dec. 29, 1943. Wounded in left lower chest by machine-gun bullet striking tangentially. Thoracotomy, splenectomy, and suture of diaphragm at F.S.U. on same day.

Jan. 9, 1944. Dullness and diminished air entry noted at right base.

Jan. 10. Forty c.c. of blood aspirated from left base. None from right base.

Jan. 14. *Admitted to Chest Centre.* General condition fair. Wounds healed. Signs suggest small effusion at both bases.

Radiograph: Minimal amount of fluid at left base and a small amount in right pleural cavity with fluid level above.

Jan. 16. Temperature rising.

Jan. 17. *Aspiration*: 7th space scapular line, right side—12 oz. thin green pus and a little air removed.

Bacteriology: *Film*—pus +++; pneumococci +++++; coliforms +. *Culture*—pneumococci ++; *B. coli* ++.

60,000 units sodium penicillin in 50 c.c. saline introduced.

Jan. 18. *Aspiration*: Right base—4 oz. yellow-green turbid fluid thinner than that obtained previous day.

Bacteriology: *Film*—pus +++; degenerate cocci +. *Culture*—*B. coli.* Penicillin, 5 units per c.c..

60,000 units sodium penicillin introduced to pleura. Temperature normal.

Jan. 20. *Aspiration*: 2 oz. thin greenish pus and much air removed.

Bacteriology: *Film*—pus +++; no bacteria. *Culture*—*B. coli.* Penicillin, 4 units per c.c.

60,000 units sodium penicillin introduced into cavity and a small amount immediately appeared in sputum.

Jan. 21. *Radiograph*: Small amount of fluid and air still present in right pleural cavity.

Jan. 22. *Aspiration*: 2 oz. pus.

Bacteriology: *Film*—pus ++; no bacteria seen. *Culture*—sterile.

FIG. 101.—Photograph of fibrin clot removed from another patient.

30,000 units sodium penicillin in 25 c.c. saline introduced.

Jan. 24. *Aspiration*: 1 oz. thick pus.

Bacteriology: *Film*—pus ++; no bacteria. *Culture*—sterile. Penicillin, 2 units per c.c.

25 c.c. 2 per cent succinyl sulphathiazole introduced to discourage Gram-negative organisms.

Jan. 27. *Aspiration*: ½ oz. glutinous pink fluid obtained.

Bacteriology: Sterile.

No penicillin.

Jan. 28. *Radiograph*: Small pyopneumothorax cavity about 2 in. in diameter remains (*Figs.* 102, 103).

Jan. 29. *Aspiration*: A few c.c. slightly turbid orange serous fluid and some air obtained.

Bacteriology: *B. coli* +.

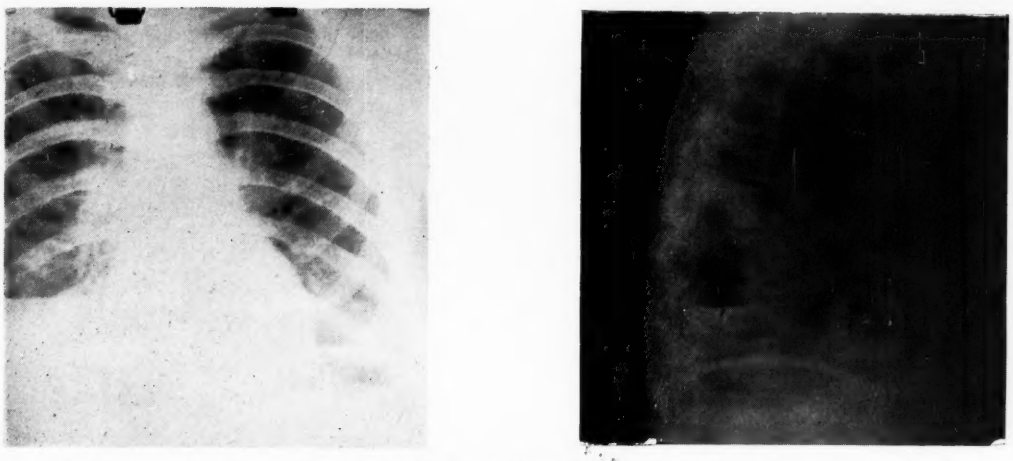
Feb. 3. *Radiograph*: No fluid seen. Air contained in cavity is smaller.

Feb. 8. Temperature 99°–100° for two days. Exploration, right base, revealed no fluid.

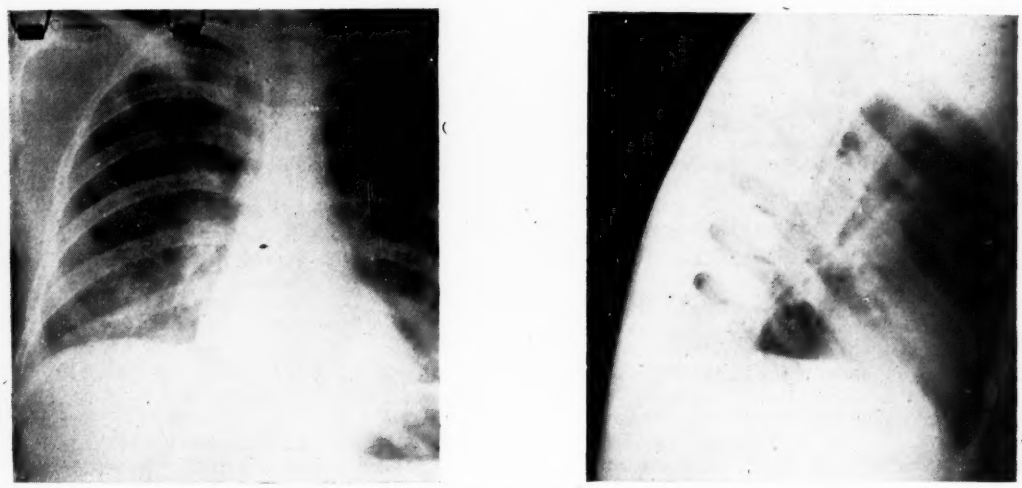
Follow-up: At 8 weeks was completely healed radiologically and clinically.

Case 24.—Section I, *Group B.* **Shell wound penetrating right chest; pyopneumothorax; pleural toilet and closed drainage. Penicillin instillations; thoracotomy and removal of metallic F.B.**

Dec. 16. 1943. Wounded in right axilla; hæmoptysis. Right hæmothorax. Patient so shocked and



FIGS. 102, 103.—*Case* 16. Posteriorly placed pyopneumothorax cavity 10 days after treatment started.



FIGS. 104, 105.—*Case* 16. Three weeks later. Cavity contains no fluid and is less than 1 in. in diameter.

Feb. 12. *Radiograph*: Cavity smaller. Small abscess in left thoracotomy wound opened. Temperature settled immediately.

Feb. 19. *Radiograph*: Cavity contains no fluid, and is less than 1 in. in diameter (*Figs.* 104, 105).

March. 2. *Radiograph*: Cavity no longer seen.

Comment.—A small right pyopneumothorax, probably secondary to a post-operative collapse, infected with pneumococci and *B. coli*, with a small bronchopleural fistula. Pneumococci disappeared from cultures after one intrapleural application. The patient was up in the ward in 2 weeks from beginning of treatment and the cavity almost disappeared within a month.

ill that there was a considerable lapse of time before he reached Chest Centre. Was staged at several units before his admission, and during that period he was aspirated 6 times and at the fourth aspiration a streptococcus was cultured from the fluid.

Jan. 13, 1944. *Admitted to Chest Centre.* General condition poor. Temperature 100·4°. Clinical signs of large right pyopneumothorax.

Radiograph: Large right-sided effusion. Large metallic F.B. near hilum of right lower lobe (18 mm. × 15 mm.) (*Figs.* 106, 107.)

Aspiration: Only a little fluid obtained because of repeated needle blockage by fibrin clots. Operation decided upon for pleural drainage and toilet.

Bacteriology of Fluid: Hæmolytic streps. +++.

Jan. 19. *Operation*: Anæsthetic—pentothal and intratracheal N_2O. 7th rib resected. Pleura opened and many fibrin clots removed. Fluid was purulent and mal-odorous. Two large pockets were present, one posterior to the lung and the other anterior to it. The lower lobe was adherent to the diaphragm in such a way as to provide an almost complete curtain between the two cavities. A pint and a half of fluid was sucked out. The lower lobe was covered by dense organizing fibrin, and this was removed by decortication. No attempt was made in the presence of such acute infection to remove the deeply-lying piece of metal. Chest closed completely and an intercostal catheter placed through the 9th space posteriorly.

Note: This was employed in place of rib resection, and the tube drainage to enable penicillin to be instilled more easily post-operatively.

Bacteriology of Pleural Pus: Hæmolytic streps. +++. Clostridia.

Post-operative Management: For 4 hours each day for 3 days, the closed drainage was interrupted and 60,000 units of sodium penicillin instilled (care being taken to prevent air passage to the pleura). A spigot was placed in the catheter and the patient placed on his left side as prone as possible. After 24 hours the temperature fell and he has remained apyrexial since (*Feb.* 15). General condition rapidly improved.

Jan. 21. *Bacteriology of drained fluid: Culture*—*B. coli*; *B. pyocyaneus*.

The lung as seen radiographically rapidly expanded. Although only intercostal drainage was employed, he was well enough to undergo thoracotomy for removal, of the F.B. on *Feb.* 21. Our usual practice is to substitute rib resection and large tube drainage by Tudor Edwards's tube after 6–10 days, as we find that intercostal drainage, though followed afterwards by immediate improvement, is not adequate for empyemata.

Feb. 19. *Radiography*: A lipiodol sinogram showed a small residual track posteriorly with an anterior pocket measuring 1·5 in. × 1 in. It was decided to drain the anterior pocket and remove the foreign body if possible.

Feb. 20. *Operation*: Pentothal and N_2O–$CHCl_3$ intratracheally. The original operation wound was re-excised; the 7th rib had not regenerated. There was no pus in the small residual cavity, but one pocket of fluid only. The lower lobe had almost completely re-expanded. Under direct radiographic control in the theatre the lobe was incised and a large metallic F.B. which lay 4 cm. deep in front of the lobe hilum was removed. The wound was partially closed after the insufflation of sulphathiazole-penicillin powder.

FIG. 106.—*Case* 24. Radiograph before drainage of the large pyopneumothorax pocket seen above. F.B. is in lung. Subsequently the F.B. was removed and this patient was completely healed clinically and radiologically a month after drainage.

FIG. 107.—*Case* 24. Radiograph taken after instillation of lipiodol into empyema pocket. This large cavity was sterilized in 2 days by penicillin instillations. (Organism was hæm. streptococcus.)

Bacteriology of Fibrin—Sterile.

Feb. 25. General and local condition extremely satisfactory.

Feb. 27. Well and apyrexial.

March 5. Very well. Up in ward. Lung re-expanded.

March 10. Up in ward. Apyrexial. Tube removed, as radiology showed complete lung re-expansion. Wound healed rapidly, and there has been a complete radiological and clinical recovery.

Comment.—This was a very satisfactory result in view of the large empyema infected by hæmolytic streptococci; in comparison with many other similar empyemata treated without penicillin, the rapid progress which enabled a difficult operation for F.B. removal to be done within a month of draining was remarkable. The apyrexial course was quite contrary to our usual experience with such empyemata due to wounds treated without penicillin.

Case 21.—Section I, *Group B*. **Crush injury of left chest. Left lung abscess (drained). Left pyopneumothorax. Aspirations and penicillin.**

Dec. 21, 1943. Crushed by a truck. Followed by gross surgical emphysema and atelectasis of the left lung and a bronchial fistula. In Forward Area

fractured 8th rib resected to remove a jagged bone end from an intrapleural tear.

Dec. 31. *Admitted to Chest Centre.* Considerable surgical emphysema. A 4-in. wound over 8th left rib was sucking and discharging foul pus.

Bacteriology of Wound : Film—pus +++ ; cocci ++. *Culture*—hæmolytic streps. +++ ; *B. pyocyaneus* + ; *B. coli* +.

Radiograph : Shallow left pneumothorax.

Jan. 2, 1944. *Operation* : When the septic wound was explored a track led through lung adherent to parietal pleura ; a bronchopleural fistula led into a lung abscess. Wound enlarged, abscess cavity opened up and drained.

In view of the infection present and the danger of a developing pyopneumothorax, a course of parenteral sodium penicillin was started.

Jan. 6. *Bacteriology of Pus from Lung Abscess : Film*—pus + ; cocci + ; coliforms +. *Culture*—*B. pyocyaneus ; B. coli.*

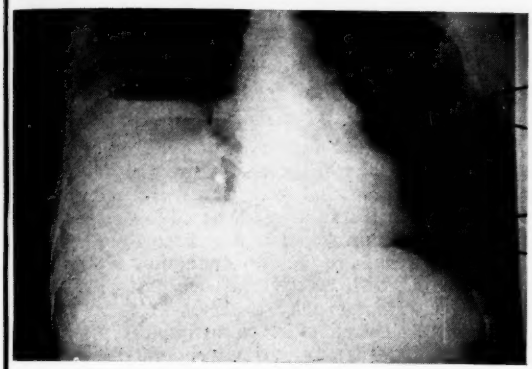


FIG. 108.—*Case* 19. Dec. 12, 1943. Radiograph showing clotted hæmothorax before treatment.

Jan. 7. Penicillin discontinuted. Total dose, 540,000 units.

Progress : By *Jan.* 9 the left lung had collapsed to the lower half of the chest. The lung abscess continued to drain freely. By Jan. 30 general condition had improved considerably. Radiograph showed partial re-expansion of both lobes, but a hydropneumothorax was present with fluid in the anterior axillary region in 3rd and 4th spaces.

Jan. 31. *Aspiration* : 1 oz. of thick greyish pus from 3rd space in the anterior axillary line. 60,000 units sodium penicillin instilled.

Bacteriology : Film—pus +++ ; Gram-positive cocci. *Culture*—no growth.

Feb. 3. *Aspiration* : 4th space anterior axillary line—1 oz. of greyish-yellow pus.

Bacteriology : Film—pus ++ ; no organisms seen. *Culture*—no growth.

The patient at this stage was afebrile for the first time for several weeks. The bronchial fistula was closed and the wound healing rapidly. A radiograph still showed air and fluid in the pleural cavity.

Feb. 9. *Aspiration* : 1 oz. of yellow serous fluid.

Bacteriology : Film—pus + ; no organisms seen. *Culture*—sterile.

Progress now most satisfactory until *Feb.* 20, when a pyrexia of 103·2° developed. Radiograph demonstrated a re-collection of fluid in the pleural cavity.

Feb. 21. *Aspiration* : 3rd space—5 oz. of thin greenish pus. 60,000 units of sodium penicillin instilled in 50 c.c. saline.

Bacteriology : Film—pus +++ ; streps. ++. *Culture*—non-hæmolytic streps.

Feb. 24. 4 oz. of thin, greenish pus. 30,000 units of sodium penicillin instilled.

Bacteriology : Culture—*Staph. albus* (contaminant).

At this stage a marked constitutional upset and fever developed.

Feb. 25. *Aspiration* : 1 oz. of thin brown pus. 30,000 units of sodium penicillin instilled.

Bacteriology : Film—many neutrophils present. *Culture*—sterile.

No further pyrexia at the time of writing (*March* 10). The wound is soundly healed and the patient is up. The present radiological appearances show a trace of fluid only remaining in the apical pocket, which is now very small.

Follow-up, April 10, 1944.—The patient is completely cured.

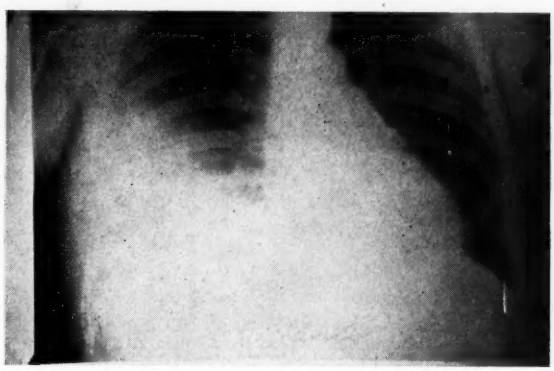


FIG. 109.—*Case* 19. Jan. 21, 1944. Radiograph prior to operation showing loculated sterile pyopneumothorax cavity.

Comment.—This patient had an anterior pyopneumothorax pocket infected from a lung abscess. When first aspirated the pus was sterile and the patient afebrile, and it is thought that the pyothorax was sterilized by the general penicillin. A re-infection took place, however, and was extinguished by one injection of penicillin. This case is interesting in view of the grave prognosis of pyopneumothorax complicating lung abscess.

Case 19.—Section I, *Group A.* **Shell wound of chest ; right empyema.**

Dec 8, 1943. Wounded by fragments of H.E. shell which penetrated pleura. Sucking pneumothorax closed at F.S.U.

Dec. 9. Signs of right hæmothorax ; 60 c.c. of blood aspirated.

Dec. 13. *Aspiration* : 1050 c.c. of blood obtained.

Dec. 15. *Aspiration* : 10 c.c. only of blood-stained fluid obtained.

Dec. 20. *Admitted to Chest Centre.* Small clean unsutured entry wound, 5th right space anterior axillary line. Trachea and apex beat to left. Dull at right base posteriorly, with weak bronchial breath-sounds and bronchophony. Impaired note at left base with weak bronchial breath-sounds and ægophony.

Radiograph : Moderate right hæmothorax. Patchy collapse of right base. Collapse of left lower lobe (*Fig.* 108).

Dec. 23. *Aspiration* : Right base—2 oz. of very thick dark blood full of clots obtained with great difficulty.

Bacteriology : Sterile.

Radiograph: Slightly less fluid. Two small F.B.'s seen in cardiophrenic angle.

Temperature 100°–102° since admission suggests that fluid is infected.

Dec. 26. *Aspiration*: (1) 8th space scapular line —2 oz. of thin, dark, serosanguinous fluid containing some clots; (2) 5th space mid-axillary line—1 oz. of pink turbid fluid.

Bacteriology: (1) Sterile. (2) Pneumococci.

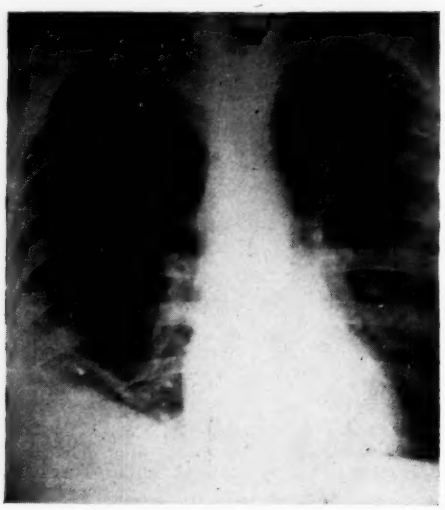


FIG. 110. *Case* 19. Feb. 20, 1944. Radiograph showing no fluid remaining. There is still pleural thickening and some elevation of the right diaphragm.

Dec. 29. Started intramuscular sodium penicillin, 15,000 units 3-hourly.

Dec. 30. *Aspiration*: 3 oz. of deep pink turbid fluid obtained from axilla.

Bacteriology: Film—red blood-corpuscles ++; pus +; diplococci ++. *Culture*—pneumococci +++.

Dec. 31. *Radiograph*: No marked change.

Jan. 1, 1944. Negative exploration in axilla.

Jan. 7. *Radiograph*: There is a well-localized collection of fluid at the right base. Left lower lobe still collapsed. Patient toxic and ill.

Sodium penicillin stopped after 1,215,000 units.

Comment.—Thirteen days' treatment with full doses of intramuscular penicillin failed to sterilize this clotted hæmothorax infected with pneumococci, but toxæmia was reduced, the temperature falling from 102° to normal for several days and appetite improved; the empyema was effectively localized. Further treatment was by intrapleural penicillin, as follows.

Jan. 11. *Aspiration*: 8th space 1 in. internal to scapular line; 8 oz. of thick chocolate pus obtained. 60,000 units of sodium penicillin in 50 c.c. saline instilled into pleura.

Bacteriology: Film—pus ++; cocci ++. *Culture*—pneumococci +++.

Jan. 13. *Radiograph*: Loculated effusion at right base remains.

Aspiration: 8 oz. of thin chocolate pus obtained. 60,000 units of sodium penicillin instilled.

Bacteriology: Film—pus +++; no bacteria seen. *Culture*—no growth. Penicillin +++.

Jan. 14. *Radiograph*: Shows less fluid.

Jan. 15. *Aspiration*: 4 oz. of chocolate fluid. 60,000 units of sodium penicillin given.

Bacteriology: Film—pus ++; no bacteria. *Culture*—no growth. Penicillin ++.

Jan. 18. *Aspiration*—5 oz. of chocolate fluid obtained and cavity washed out with saline through needle; much clot and debris obtained.

Bacteriology: Film—pus ++; no bacteria. *Culture*—no growth. Penicillin ++.

Radiograph: Slightly less fluid (*Fig.* 109).

Jan. 21. *Operation*: Minor thoracotomy through 7th right intercostal space. Pleura moderately thick. Three-quarters of a pint of thick pus sucked out, and very large fibrinous clots removed. 30,000 units of sodium penicillin instilled. Complete chest closure without drainage.

Bacteriology of Fibrin: Film—pus +; no bacteria. *Culture*—*B. coli* scanty.

Bacteriology of Pleural Fluid: Film—no pus or bacteria. *Culture*—no growth.

Jan. 24. *Aspiration*: 2 oz. of slightly turbid fluid removed.

Bacteriology: Film—pus +. *Culture*—no growth. Penicillin +++.

Jan. 27. *Aspiration*: 3 oz. of red serosanguinous fluid obtained.

Bacteriology: Culture—sterile.

Jan. 28. *Radiograph*: Empyema cavity no longer seen. Dense fibrous-looking shadow in right basal region remains, with peripheral elevation of diaphragm. Still left lower lobe collapse.

Jan. 29. Exploration, but no fluid found.

Feb. 1. *Radiograph*: no change.

Feb. 8. Afebrile. Apyrexial for past 7 days. Up.

Feb. 20. *Radiograph*: *See Fig.* 110.

March 6. Evacuated as a sitting case.

Comment.—Hæmothorax infected with pneumococci sterile after first injection of 60,000 units of sodium penicillin. Minor thoracotomy performed for clearance of clot. Up and afebrile with all fluid absorbed within two months of wounding and one month of first intrapleural instillation.

SECTION II.—PENICILLIN USED AS A PROPHYLACTIC AGENT

As the patients with simple hæmothorax usually arrived at this Chest Centre some days after being wounded, it was not possible at this level to estimate the value of penicillin in the prevention of infection. The hæmothoraces that reached this Centre uninfected rarely became infected, and if such were used in an investigation little information of value would be obtained. Our chief opportunity of using penicillin to prevent pleural infection has been after thoracotomy for the removal of pulmonary and pleural metallic foreign bodies. The cases are grouped as follows:—

After Thoracotomy and for Uninfected Hæmothorax.—

Group A.—Treated by parenteral sodium penicillin—3 cases.

Group B.—Treated by intrapleural sodium penicillin instillations—5 cases.

Group C.—Treated by the insufflation of penicillin-sulphathiazole powder—4 cases.

These thoracotomies were done for the removal of foreign bodies. A serious complication of such operations is the development of post-operative effusions which may become infected.

The usual routine, whether penicillin is used or not, has been to avoid drainage tubes and to rely on post-operative aspirations. Any measure that can prevent infection of the effusion is of great value.

In this series of 202 chest wounds 43 operations were done for the removal of intrathoracic foreign bodies of 1 cm. or more. Seventeen of the 43 cases received penicillin and 26 did not. In the one pencillin-treated case which became infected (*Case* 30), the infection developed late, due to the surgical conditions present, and was not attributable to penicillin failure. As only 4 of the 26 cases which did not receive penicillin became infected, the figures have little statistical value, but the case-histories of the treated cases offer a far better picture.

DISCUSSION

Seventeen operations have been done for the removal of foreign bodies, with development of severe post-operative infection in one, the result of a huge broncho-pleural fistula. In the early days of our use of penicillin we employed parenteral therapy: we now consider this unnecessary. It is recommended that after foreign body removal from the lung the area should be insufflated with sulphathiazole powder before suture and that 15,000–30,000 units of sodium penicillin be left in the pleural cavity, followed by complete chest closure without drainage. If effusions develop post-operatively, these should be thoroughly aspirated and the removed fluid submitted for bacteriological examination; should Gram-positive pyogens appear, then the treatment by penicillin intrapleural injections as described earlier should be employed. We feel now quite convinced that intrapleural therapy is far better than parenteral therapy, both therapeutically and prophylactically.

CASE REPORT

One case-history, as follows, indicates the line of treatment.

Case 32.—Section II, *Group B.* **Shell wound of left chest. Pulmonary F.B. Lobectomy.**

Dec. 18, 1943. Wounded. Negative laparotomy done in Forward Area because of abdominal signs or rigidity, etc. Later a left hæmothorax was noted (*Fig.* 111).

Dec. 31. *Admitted to Chest Centre.* General condition good. Small clean entrance wound on 4th left space in mid-axillary line.

Radiograph: A very shallow hæmothorax and a metallic F.B. (8 mm. × 7 mm.) near the hilum of the left lower lobe.

Although this F.B. was smaller than that usually selected for operation, thoracotomy was decided upon because of its dangerous site—i.e., near the hilum.

Jan 13, 1944. *Operation*: Pentothal and N_2O–$CHCl_3$ intratracheally. Major thoracotomy through bed of resected 7th rib. Lower lobe showed partial atelectasis, and there were massive adhesions present. The mobilization of this lobe was very difficult. The F.B. lay in close apposition to the main left lower bronchus, to which it was joined by inflammatory tissue: in the course of separating it from the affected bronchus the latter tore widely. A left lower lobectomy was the only satisfactory treatment, and this was done by tourniquet method. The F.B. lay in a small abscess cavity containing much battledress. The

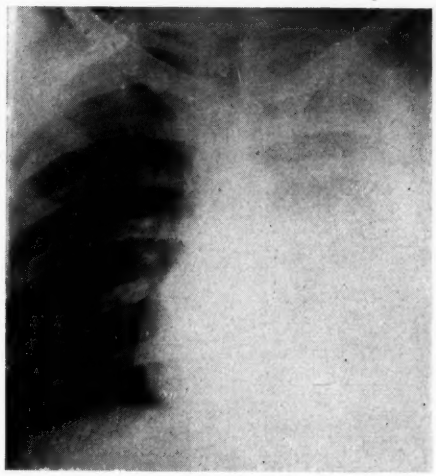


FIG. 111.—*Case* 32. Radiograph showing left hæmothorax before admission to Chest Centre.

chest was closed without drainage and 30,000 units of sodium penicillin were instilled.

Bacteriology of Abscess Cavity: Culture—Staph. aureus +; *Staph. albus* +.

Progress: General condition good throughout.

FIG. 112.—*Case* 32. Radiograph 2 days after left lower lobectomy: upper lobe collapsed; hydropneumothorax. Treated by aspiration and penicillin instillations.

Jan. 15. *Aspiration*: 32 oz. of blood-stained fluid.

Bacteriology: Culture—no growth. 30,000 units of sodium penicillin instilled.

Jan. 17. *Aspiration*: 14 oz. of fluid obtained. 30,000 units of sodium penicillin instilled.

Bacteriology: Culture—Staph. albus. Penicillin, 2 units per c.c.

Jan. 19. *Aspiration*: 18 oz. of serous fluid. 30,000 units of sodium penicillin instilled.

Bacteriology : Culture—sterile. Penicillin, 2 units per c.c.

Jan. 21. *Aspiration*: 8 oz. of serosanguinous fluid. 30,000 units of sodium penicillin instilled.

Bacteriology : Culture—sterile. Penicillin, 3 units per c.c.

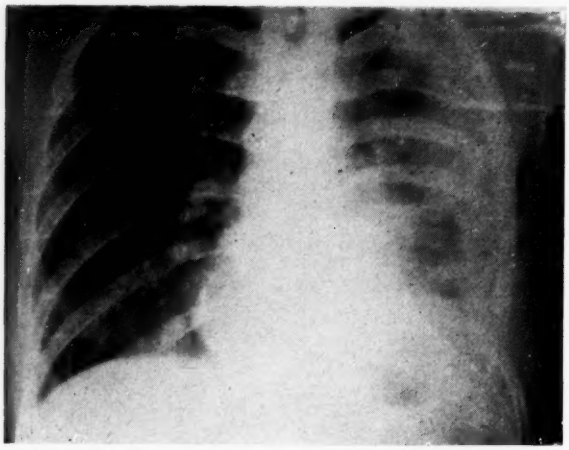


FIG. 113.—*Case* 32. Radiograph 3 weeks after lobectomy. Upper lobe expanding well. Effusion remained free from Gram-positive organisms and treated by aspiration. At time of writing (*March* 14, 1944) patient up and well, and there is no fluid radiographically. Follow-up, *April* 1, 1944: Completely well—no fluid or empyema cavity left.

Jan. 23. *Aspiration*: 5 oz. of fluid.

Bacteriology : Culture—sterile. Penicillin, 2 units per c.c.

Wound has healed by first intention. It is interesting to note that this pleural cavity, 10 days after septic operation of tourniquet lobectomy, remained sterile.

Jan. 25. *Radiograph*: Expanding upper lobe, but several pockets of fluid.

Aspiration: 4 oz. of serosanguinous fluid.

Bacteriology : Film—pus +, but no organisms. *Culture—Staph. albus.* Penicillin 2 units per c.c. 30,000 units of sodium penicillin instilled.

Jan. 27. *Aspiration*: 1 oz. of fluid and 300 c.c. of air.

Bacteriology : Culture—sterile. Penicillin 5 units per c.c.. 30,000 units of sodium penicillin instilled.

Radiograph: Still some pocketing. Left upper lobe expanding well.

Jan. 29. *Aspiration*: No fluid obtained, but 100 c.c. of air removed.

Jan. 30. Patient up in ward.

Feb. 4. Patient coughing up a little brownish fluid. A bronchial fistula has developed as revealed by aspiration of 3 oz. of similar fluid in pleural cavity. 60,000 units of sodium penicillin instilled, and a little was coughed up.

Bacteriology : Culture—B. pyocyaneus ++; on penicillin.

Feb. 7. General condition good. Still coughs up a little fluid.

Aspiration: 20 c.c. of thick brownish pus.

Bacteriology : Culture—B. pyocyaneus ++. No penicillin; 40 c.c. of 2 per cent succinyl sulphathiazole instilled in hope of inhibiting Gram-negative organisms.

Feb. 11. *Aspiration*: 2 oz. of yellow serous fluid from anterior pocket.

Bacteriology : Culture—sterile. No penicillin.

Aspiration: 1 oz. of thin yellow-brown pus from posterior pocket. Instillation of 10 c.c. of 2 per cent succinyl sulphathiazole solution.

Bacteriology : Culture—B. pyocyaneus ++; *B. coli* +. No penicillin.

Feb. 15. *Aspiration*: posterior pocket—20 c.c.

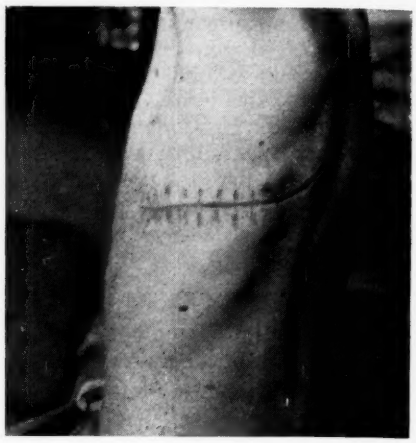


FIG. 114.—*Case* 32. Healed thoracotomy wound after lobectomy by tourniquet method. No post-operative drainage. Post-operative effusion treated by aspiration and penicillin instillations. Gram-negative pus developed and was removed by aspiration.

of chocolate-brown pus and instillation of 5 c.c. succinyl sulphathiazole solution.

Bacteriology : Culture—B. pyocyaneus ++. No penicillin.

Feb. 20. Upper lobe has expanded to fill all the left chest except for small basal area.

Feb. 21. *Aspiration*: 5 c.c. of yellow fluid. 10 c.c. of succinyl sulphathiazole solution instilled.

Bacteriology : Culture—B. coli +; *B. pyocyaneus* +.

Feb. 24. *Aspiration*: 5 c.c. of yellow fluid. 10 c.c. of succinyl sulphathiazole solution instilled.

General condition very good. Up and about ward.

March 10. Upper lobe has expanded to fill most of the hemithorax. Minimal effusion. Up and well.

Comment.—It is unusual for a lobectomy done by the tourniquet method to escape Gram-positive coccal infection. This pleural cavity has remained free from serious infection, and drainage by operation has been avoided. The Gram-negative infection did not cause constitutional disturbance. There is a good deal of evidence in this instance to support the value of penicillin as a prophylactic agent, and drainage by rib resection has been avoided.

SECTION III.—LOCAL PENICILLIN IN SEVERE CHEST-WALL WOUNDS

Experience with the penicillin technique for the closure of septic war wounds in other areas of the body made us increasingly confident in using it. In chest-wall wounds three serious problems are often present :—

1. The coexistence of a serious intrapleural lesion or of an extrapleural hæmothorax (a collection of blood-stained fluid in the plane of the endothoracic fascia).

2. The association of open fracture of the ribs and scapula with the soft-part wounds.

3. The serious consequences that follow the breakdown of a chest-wall wound so that a septic open pneumothorax develops. We have always regarded this as a most grave complication. Before penicillin was available such patients required drainage of the infected pleural cavity while the attempt was made to close the septic sucking wound by large vaseline pads—an ineffective closure. Such septic wounds can be closed with penicillin without any fear of a developing chest-wall cellulitis. Similarly, sucking wounds that have been closed in a Forward Area by the pad method can be sutured on arrival at Chest Centres with the aid of penicillin. This restores the normal mechanics of the chest.

The cases detailed herewith were all infected wounds, few, if any, of which we should have been prepared to close without the use of penicillin. This is important to note. It has been quite impossible to furnish control cases because suture of these wounds with any sulpha drug would have been dangerous surgery. All these wound closures were done eight or more days after wounding.

Group A. Complete Suture with Calcium Penicillin Instillations through Small Rubber Tubes.—The wounds were débrided and the skin edges freshened. The wounds were sutured with vertical mattress sutures and instillation tubes were laid in the recesses of the wounds through separate para-incisional stab wounds (*Fig.* 115). Two to three c.c. of calcium penicillin solution, 250 units per c.c., were instilled into each tube at 12-hourly intervals for 3 to 5 days. Chest wall abscesses were thoroughly opened up, pus mopped out, and a minor débridement done. The abscess cavity was then closed by suture, as below. Where rib was seen denuded of periosteum in the region of fractures, a resection of the devitalized bone was usually done. Most of these operations represent the treatment of open septic fractures by suture with the use of local penicillin.

FIG. 115.—The instillation tube method. A septic chest-wall wound has been excised and sutured: three para-incisional instillation tubes have been placed in the wound: through one of the tubes calcium penicillin is being injected. The first instillation is made in the theatre, and instillations are repeated 12-hourly for 3 to 5 days.

Group D. Local Penicillin Treatment of Lesions Deep to the Rib Plane, Extrapleural Hæmothorax, Lung Abscess, Localized Intrapleural Effusions.

Extrapleural Hæmothorax.—This is a condition with which we are becoming increasingly familiar. It is usually associated with a fracture of the ribs and the presence frequently of a metallic fragment deep to the rib plane; blood strips up the plane of the endothoracic fascia without entering the pleural cavity. Such fluid is liable to infection. If unassociated with a foreign body it is treated by aspiration, but the space is opened up if the missile has to be removed. From a reasonable experience of such operations we have learnt to regard them as anything but trivial, and in our contrast series of non-penicillin-treated cases we have seen infection develop frequently. As the cavity is a localized one, it was hoped that calcium penicillin locally would arrest or prevent infection.

CASE REPORTS

Case 43.—Section III, *Group A.* **Gunshot wound (rifle), tangential, left chest; open fracture of the ribs and costal cartilage; small hæmothorax; pneumoperitoneum; paradoxical respiration.**

Jan. 4, 1944. Wounded, but not picked up for 2 days.

Jan 4. *Operation at F.S.U*: Septic chest-wall wound. Wound which passed from over 4th left space obliquely downwards to end in the left lumbar region. The whole track was opened up and seen to be infected throughout. In its path lay comminuted fractures of 6th, 7th, 8th, 9th, and 10th costal cartilages and 8th and 9th ribs. A small open sucking pneumothorax was present in 8th space. Two pieces of bullet casing and several loose fragments of rib and cartilage were excised. Wound left widely open.

Jan. 13. *Admitted to Chest Centre.* General condition poor, with left-sided paradoxical breathing causing severe dyspnœa. This latter factor made it very important to secure union and fixation of the severe chest-wall fracture.

Radiograph: Shallow left hæmothorax. Small metallic F.B.'s in left chest wall. Fracture of ribs, left chest. A small amount of air below diaphragm (pneumoperitoneum).

Jan. 14. *Operation*: Pentothal and intratracheal N_2O. Huge gaping wound 26 in. long and 3 in. wide at its centre (*Fig.* 116). The longest wound we have seen. Obvious sepsis present with open fracture of many ribs and cartilages. Minor débridement done—no skin removed. Under very considerable tension the wound was closed with 5 instillation tubes left in situ (*Fig.* 117). Before suture sulphathiazole-penicillin powder was insufflated.

Bacteriology: Film—pus +; coliforms +. *Culture—B. coli* ++; diphtheroids +.

Progress: Coincidentally with 12-hourly instillations for 5 days into the wound, the hæmothorax was dealt with by aspiration and sodium penicillin instillations. The wound received in all 32,500 units of calcium penicillin. Sutures were retained for 14 days and the wound has remained soundly healed (*Fig.* 118).

Radiograph: Foreign body 18 mm. × 10 mm. in 7th space deep to ribs. There is an abscess cavity with a fluid level around the fragment. The 7th rib is fractured.

FIG. 122.—Case not described in the text. This lesion represents one of the major complications of war wounds of the chest. He was admitted 10 days after being wounded, with a huge open septic pneumothorax accompanied by a pyopneumothorax. The latter was drained by rib resection below the wound which was re-excised and partly sutured (penicillin was not available at that date). The suture was a complete failure and occlusion by vaseline gauze was required for 8 weeks before the wound closed in its depths as shown above. The lung remained incompletely expanded after 4 months. No such breakdown has occurred in the penicillin sutured closure of equally serious wounds in the series described in this report.

Operation: Pentothal and intratracheal N_2O. Resection of 7th rib. Foreign body removed from a small intrapleural pocket of fluid from which led a track into a lung cavity containing pus and air, and in the depths of which lay a small bronchial fistula. The pus was mopped out and two penicillin instillation tubes laid into the lung cavity. Another tube was placed in the muscle layer which was loosely sutured with catgut. Complete skin closure.

Bacteriology of Cavity: Staph. aureus and (?) pneumococci.

Progress: 12-hourly calcium penicillin instillations for 3 days—total dosage 9000 units. An uneventful convalescence leading to first-intention wound healing. Sutures out on *Jan.* 10, 1944. Well and symptomless.

Jan. 12, 1944. *Radiograph*: No evidence of abscess cavity. Slight overlaying pleural thickening.

Jan. 15. Evacuated as an up-patient.

Comment.—A very satisfactory result. Complete suture of such a wound is against all the principles of lung abscess surgery, especially in view of the bacterial flora of the cavity. Had penicillin not been available, this wound would have been left open with a light pack in the cavity, and convalescence would have been correspondingly slow.

SECTION IV.—EXTENSIVE SEPTIC CHEST-WALL WOUNDS SUTURED WITH THE ASSISTANCE OF PARENTERALLY-ADMINISTERED SODIUM PENICILLIN

The closure of a septic open sucking wound, usually associated with a pyopneumothorax, is of prime importance.

The object of treatment in such a case is to drain the empyema or aspirate the infected hæmothorax and to obtain rapid lung expansion. The closure of the sucking wound is of great importance. Before the advent of penicillin such a wound could only be closed by vaseline gauze packing, since suture in the presence of sepsis was usually a failure. The pack method has many obvious disadvantages. We believe that penicillin has provided the solution to this hitherto difficult problem.

CASE REPORTS

Case 60.—Section IV. **Thoraco-abdominal shell wound. Left hæmothorax. Septic chest-wall wound.**

Dec. 23, 1943. Wounded. Large sucking wound left subcostal area. Operated on 16 hours later by Major Mills, R.C.A.M.C., who, by a combined thoraco-abdominal incision, removed a lacerated spleen and repaired two diaphragmatic tears. The patient made a magnificent recovery.

Jan. 9, 1944. *Admitted to Chest Centre.* General condition good. A healed left Kocher's incision. The left chest had a septic wound in the 7th space mid-axillary line and a septic wound over in the 7th space mid-axillary line and a septic wound over the 12th left rib in the posterior axillary line.

Radiograph: Moderate-sized left pleural effusion.

Jan. 12. *Aspiration*: 12 oz. of hæmothorax fluid aspirated.

Bacteriology: Culture—sterile.

In view of the sterile hæmothorax, it was felt that every effort must be made to prevent the further breakdown of the two purulent wounds and thus prevent the risk of empyema formation.

Operation: Pentothal and N_2O. Both wounds contained dead rib in their bases. A track full of pus led from one wound to the other. This track was opened up and several segments of white dead rib removed. Complete wound suture with 4 penicillin instillation tubes.

FIG. 123.—*Case* 60. Result after closure of a septic chest-wall wound infected by *Staph. aureus* and hæmolytic streptococcus.

Bacteriology: Culture—Staph. aureus +; Hæm. streps. +; *B. proteus.*

Progress: It was decided that calcium penicillin should be instilled 12-hourly for 5 days in view of the serious wound infection.

Jan. 17. All tubes blocked and fluid could not be instilled. Total dosage given, 12,000 units.

In view of the importance of obtaining sound union, it was decided to treat the patient with parenteral sodium penicillin, and 21 injections of 15,000 units at 3-hourly intervals were given. Total sodium penicillin dosage, 315,000 units. Sutures were retained for 11 days. Complete healing by first intention. No fluid in left chest. Patient up and about the ward (*Fig* 123).

Comments.—This may appear to be an extravagant use of penicillin. The consequences of an empyema developing would have been serious, and in view of the grave lesions from which this patient had been saved by the previous surgery we felt fully justified in using so much penicillin. At the time of writing (*Feb.* 15, 1944) this patient has made a complete recovery.

Case 61.—Section IV. **Shell wound left chest. Thoraco-abdominal injury. Severe chest-wall wound. Pyopneumothorax.**

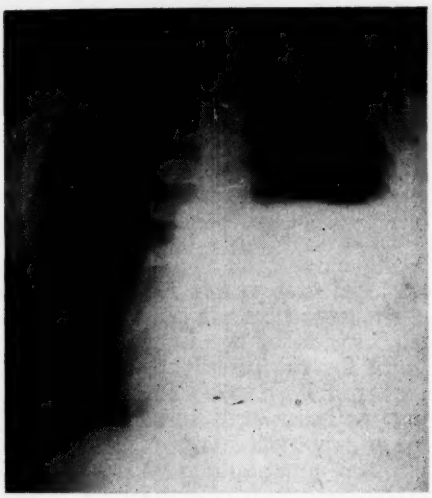


FIG. 124.—*Case* 61. Radiograph of left pyopneumothorax. Pus was dribbling out of a completely broken-down thoracotomy wound. This wound was sutured in the presence of gross infection and first intention healing followed.

Jan. 5, 1944. Wounded. Admitted to F.S.U. Torn and lacerated diaphragm visible through huge wound of left lower ribs. Thoracotomy and splenectomy; suture of diaphragm. An astonishing recovery and operative result.

Jan. 19. *Admitted to Chest Centre.* General condition fair. Clinical signs of left pyopneumothorax. Here only the wound management is described. A huge gaping wound, 8 in. × 5 in., present over the postero-lateral aspect of left lower ribs. There is dead white rib exposed in its depths and much thick pus was present.

Radiograph: Left pyopneumothorax (*Fig.* 124). Lung well collapsed. Fractured ribs.

Operation: Pentothal and N_2O intratracheally. Portion of two ribs denuded of periosteum resected. Skin edges freshened and pus mopped away. Much of this pus was leaking into the wound from the empyema. The wound was completely sutured with three penicillin tubes left in it. The 8th rib was then partially resected. One and a half pints of offensive pus were sucked out and closed Tudor Edwards's drainage instituted.

Bacteriology: Culture—Staph. aureus ++. Clostridia.

Progress: In view of the grave character of the wound and the serious consequences of the breakdown of the huge open sucking pneumothorax wound, it was decided to place the patient on a full parenteral sodium course, and at the same time to apply local penicillin treatment. The reason for this apparent extravagance is that we wished to maintain a large local concentration of the drug in this grossly infected wound, which was really a part of a large abscess cavity. Penicillin dosage—local calcium penicillin 18,000 units; general sodium penicillin, 750,000 units. The effect of this latter is discussed in *Section* I, *Group A.*

The sutures were held for 12 days, and the wound healed by first intention and has remained so to the time of writing (*March* 10), 1944). (*Fig.* 125.)

Follow-up, April 10, 1944: Remains healed and well; empyema healed clinically and radiologically.

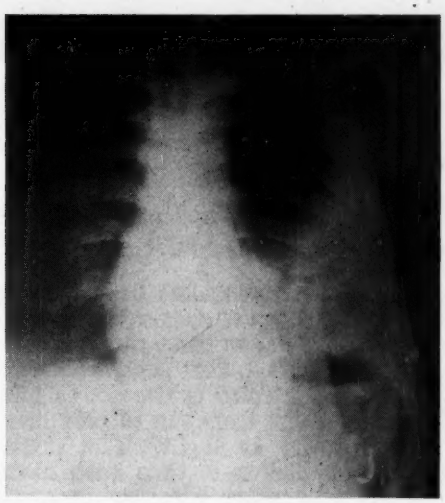


FIG. 125.—*Case* 61. Radiograph two weeks after drainage of pyothorax shown in *Fig.* 124. This drainage was done above a large septic wound closed with penicillin, which healed in spite of the unfavourable condition.

Comment.—A noteworthy result which could not have been obtained without the use of penicillin. Without the help of penicillin the primary suture of a gaping septic open pneumothorax situated at the base of an empyema cavity would be a severe violation of all surgical principles and would be followed by failure.

CONCLUSIONS

Out of a series of 202 severe chest wounds penicillin therapy has been employed for 64.

Comparison of the results in those which received penicillin and those which did not leaves no doubt about the value of penicillin therapy in war wounds of the chest. Most of the work has been done on established chest infections, and the most satisfactory results have been obtained in two main groups.

1. *In cases of pyotharax.* The treatment of pleural infection by intrapleural injections or

instillations has been far more useful than treatment by parenteral penicillin therapy. In only one of the cases treated by the former method was there failure to control infection, even in the presence of thick offensive pus. For the first time in our combined experience thoracic empyemata have been cured without surgical drainage.

FIG. 126.—*Case* 62. A large septic chest-wall wound which was used for anterior thoracotomy for removal of pleural missile. The wound was infected with *Staph. aureus*, but was successfully sutured with the help of penicillin. Details not given in text.

FIG. 127.—*Case* 62. Wound shown in *Fig.* 126, after penicillin closure with three instillation tubes in place.

A remarkable finding has been the capacity of the pleural cavity to retain instilled sodium penicillin for as long as three days; this means that a reservoir of the best known bacteriostatic agent can be maintained at the site of infection. Conversely, passage from the blood-stream into the pleural cavity is slight. The method of intrapleural instillation is thus both more economical and far more effective than that of parenteral therapy, besides being less disturbing to the patient.

2. *In cases of severe chest-wall wounds and certain lesions deep to the rib plane.* By penicillin administered 12-hourly through instillation tubes the most septic chest-wall wounds have been closed without drainage and with a high degree of success. The method solves one of the chief problems in war wounds of the chest and will prove invaluable in the closure of the serious open septic pneumothorax wound. Such a closure is in every way preferable to pad occlusion by vaseline gauze at Base Hospital level.

Penicillin has been given locally for such conditions as extrapleural hæmothorax, and localized intrapleural hæmothorax encountered during thoracotomy operations. The chest can then be closed confidently without drainage. One lung abscess was treated with complete success by suture combined with penicillin instillations, and first intention healing was obtained.

In the more severe cases parenteral penicillin is required. It is important to note that even in the presence of gross sepsis associated with ribs devoid of periosteum union by first intention is obtainable.

3. Systemic therapy should also be given for the occasional case where in spite of adequate surgical drainage toxæmia persists as a result of bacterial invasion of the lung or pleural membrane, and for the occasional severe chest-wall wound where failure to obtain closure of a septic open pneumothorax wound would endanger life.

4. As a prophylactic agent against infection, penicillin is of great value and has been used in major thoracotomy operations with satisfactory results. It is recommended that in the forward areas the attempt to prevent infection of hæmothoraces should consist of thorough aspiration combined with penicillin instillations. This would appear to offer the best hope of preventing the present high rate of hæmothorax infection seen in this theatre of war.

5. Penicillin therapy will sterilize most pleural effusions. Since it does not prevent the mechanical derangements of a hæmothorax, adequate aspiration and surgical measures (such as thoracotomy) are still required, but these are safer procedures when carried out in a pleural cavity freed of Gram-positive pyogens by previous penicillin therapy. To obtain good results the closest co-operation between physician, surgeon, bacteriologist, and radiologist is essential.

6. There were no deaths in 64 cases. In a contrast series there were 6 deaths in 40 cases. Penicillin reduces the mortality and period of invalidism after chest wounds.

PENICILLIN IN HEAD AND SPINAL WOUNDS

By HUGH CAIRNS, Brigadier, R.A.M.C.

Virtually all gunshot wounds of the head are infected with pyogenic bacteria. In the absence of adequate operative treatment within a reasonable time the result is usually a suppurating wound. In non-penetrating wounds (i.e., with the dura intact) if the bone is involved local osteomyelitis and sequestrum formation are common, and the wound discharges pus continuously or intermittently, sometimes for months, until the dead bone is removed. In penetrating (brain) wounds infection develops in the brain substance, usually appearing first in the superficial layers of the wound and spreading inwards. The result is a brain abscess or spreading purulent encephalitis, often associated with fungus and followed by purulent ventriculitis, meningitis, and death. In orbito-frontal wounds meningitis may arise without intervening brain abscess or ventricular infection. In the majority of head wounds examined bacteriologically by Major Scott Thomson during the Sicilian campaign *Staphylococcus aureus* was found, hæmolytic streptococcus and pneumococcus being also obtained in a few cases; with the exception of the occasional resistant strain of *Staph. aureus*, all of these were susceptible to penicillin.

Penicillin was first used in recent head wounds during the battle of Sicily by neurosurgical units under the command of the late Major K. C. Eden and Major J. Shoreston (Cairns, Eden, and Shoreston, 1943). Subsequently, during the Italian campaign, many more cases were treated, but detailed reports of this work are not yet available. Meanwhile, in the United Kingdom experience has been gained in the use of penicillin in the treatment of pneumococcal and other forms of meningitis, and this has some application to the treatment of head wounds.

To what extent penicillin will pass from the blood-stream into brain tissue is not at present known, but it does not pass freely into the cerebrospinal fluid, either in the cat (Abraham et al., 1941), or in man (Cairns, Duthie, Lewin, and Smith, 1944). Hence, to combat infection in head wounds, penicillin must be administered locally. The drug is innocuous, both within the brain substance and in the cerebrospinal pathways, in concentrations well above those required to inhibit the growth of sensitive organisms.

Preparations.—

1. Undiluted penicillin powder applied to the rabbit's brain excites a certain amount of cellular necrosis and leucocytic reaction (Russell, 1944). With sulphanilamide or sulphathiazole as a vehicle, calcium penicillin has been applied to brain wounds as a powder in strengths of 1000 to 5000 units per gramme. After surgical toilet and hæmostasis, the whole surface of the wound is frosted with powder by means of an insufflator. For the average wound 1 g. of powder suffices, and particular care should be taken that this powder is not washed away by hæmorrhage from the wound. Sulphathiazole is probably a better vehicle than sulphanilamide because it is more slowly absorbed; in recent brain wounds as Ascroft (1943) found, it does not have the epileptogenic effect which Watt and Alexander (1942) and Pilcher et al. (1942) observed when they applied it to the healthy animal cortex and to wounds during operations for intracranial tumour in man. Preliminary experiments suggest that sulphamezathine will also make an excellent vehicle (Russell, 1944).

In the Forward Area repeated instillations of penicillin solutions into wounds is impracticable, and the tendency is to close head wounds completely after excision and a single application of powder. In such circumstances the stronger preparations of penicillin are to be preferred.

2. Sodium or calcium penicillin solutions are instilled into brain wounds through tubes. The early work was done with solutions containing 250 units per c.c., but increasing experience has shown the need to reduce the amounts of fluid injected into brain wounds when they are healing, and stronger solutions, up to 1000 units per c.c., have since been employed.

For intraventricular, cisternal, or lumbar injection in cases of ventricular and meningeal infection, solutions containing up to 2000 units per c.c. of the purer preparations containing 500 units of penicillin per mg., which are now available, can be used with safety. One batch of penicillin which we employed produced a sterile pleocytosis and short-lived symptoms of meningitis. Therefore each fresh batch of penicillin should at first be injected intrathecally with caution.

In all instillations into the cerebrospinal pathways the strictest aseptic precautions should be observed to avoid introducing Gram-negative organisms. Solutions are passed through a Seitz filter and are issued in small bottles, one for each patient.

3. Systemic injections of penicillin (15,000 units 3-hourly, or a continuous intramuscular drip at the rate of 5000 units hourly) are required in cases of gunshot wound of the head in which there develops a spreading infection of the soft tissues, the skull, or the venous sinuses.

When we consider what part penicillin may play in preventing or eradicating the infective complications of head wounds it is important not to lose sight of the fact that the major factor in treatment is the surgical removal, at the earliest possible moment, of infected material and necrotic tissue, and especially the indriven fragments of bone (Ascroft, 1943). In the North African campaigns, before the days of penicillin, the establishment of facilities for expert operative treatment within 48 hours of the time of wounding halved the incidence of brain abscess and other intracranial infections (Ascroft, 1943; Eden, 1943). Infective complications still arise because of the difficulty of thoroughly cleaning the brain

wound: the wound is often a narrow track extending deeply, and perhaps crossing a fissure, and it requires gentle handling if uncontrollable hæmorrhage is to be avoided. It is a matter of experience that chips of indriven bone may be left behind even after careful débridement

Table I.—PENETRATING

Case No.	Wound				Previous Treatment			Present Treatment			Bacteri-	
	Site	Age (Days)	Purulent	Fungus	Operative	Local Sulphanilamide	Systemic Sulphanilamide	*Operation (Material Removed)*	*Penicillin (Local Solution unless Stated)* Amount	Days	*At Operation* Gram-positive Pyogens	Others
1	L. temporal	3+	+		+	+	S.A., 8 g.	Bone chips and débris. M.F.B. not removed	12,000	5	*Staph. albus*	*E. coli*
2	L. frontal	3+			+		S.P., 10 g.	8 c.c. diffluent brain tissue and clot	20,500	4	Gram-positive cocci (Film only)	Coliform
3	L. frontal	3+				+	+	Bone chips	10,500	3	*Staph. albus*	*Ps. pyocyanea*
4	R. frontal	3+	+		+	+	S.D., I.V., 9 g.	Clot and bone chips	25,000 315,000 I.M.*	5 3½	*Staph. aureus*	*E. coli* D's
5	L. orbito-temporal	3½				+		Roof of orbit, pulped brain	2,250	3	Sterile	Sterile
6	R. parietal	3½			+	+	S.A., 1 g. 4-hourly	Clot, bone chips, and hairs. M.F.B. not removed	2,750	3	*Staph. aureus*	—
7	R. fronto-temporal	4	+		+		S.P., 12½ g.	Metal, bone chips, blood-clot, necrotic brain and temporal muscle	34,500	5	*Staph. aureus* Non-hæm. Strep.	—
8	L. parietal	5		+	+		S.D., I.V., 12 g.	Bone chips and necrotic brain	12,250	4	Non-hæm. Strep.	—
9	L. cerebellar	5+						Metal F.B., bone chips	11,500	4	Non-hæm. Strep.	*Ps. pyocyanea*
10	L. occipital	5+	+	+				Fungus, pus, and bone chips	9,750	2½	*Staph. albus* *Staph. aureus* Non-hæm. Strep.	*Ps. pyocyanea*
11	R. orbito-temporal	5½	+				S.P., 14 g.	R. eye. Tip of mastoid	9,750	4	*Staph. aureus*	*E. coli*
12	L. occipital	5½			+	+		Necrotic brain	13,000	3	*Staph. aureus*	—
13	L. temporal	6					S.P., 9 g. S.D., I.V., 6 g.	Bone chips and blood-clot	12,000	4	*Staph.* †	—
14	Mid-frontal	6+						Bone chips. M.F.B. not removed	6,000	4	*Staph. aureus* Hæm. Strep.	Anthracoids
15	R. frontal	6	+		+		+	M.F.B. Ulcerated galea, bone chips, and clot	23,000	4	*Staph.* †	Clostridia tetanus, *E. coli* *Ps. pyocyanea*
16	Bi-frontal	7	+				Sulpha 15 g.	Abscess in temporal muscle, necrotic brain, loose bone fragments	40,000	7	*Staph. aureus* *Staph. albus*	*E. coli* D's enterococci
17	L. frontal	8	+	+	+	+		Fungus, bone chips, hairs, and three brain abscesses	15,000	2	*Staph. albus* Pneumococci	*Proteus*
18	R. frontal	8	+		+	S.A. 10 g.	S.D., I.V., 23 g.	Pus, bone chips, and necrotic brain	5000 485,000 I.V. or I.M.*	5 5	*Staph. aureus*	—
19	L. occipital	8+	+	+	+	+	S.T., 34 g.	Fungus, bone chips, and pus	9,000	6	*Staph. aureus*	—
20	L. parietal	10					S.A., 1 g. 4-hourly	Bone chips and old blood. M.F.B. not removed	9,000	5	No	record
21	R. occipital	10	+		+	+		Pus, bone chips, necrotic brain and clot. M.F.B. not removed	10,000 505,000 I.M.*	4 5	*Staph. aureus*	—
22	L. temporal	11+	+		+	+		Temporal muscle, extradural clot, and intracerebral bone chips	15,000	6	*Staph. aureus*	Enterococci
23	L. temporal	12	+		+	+	S.D., I.V., 39 g.	Abscess of temporal muscle, intracerebral bone chips. M.F.B. not removed	7,000	4	*Staph. aureus*	*E. coli* *Ps. pyocyanea*

S.P., Sulphapyridine
S.A., Sulphanilamide
S.T., Sulphathiazole
S.D., Sulphadiazine

M.F.B., Metal Foreign Body
I.V., Intravenously
I.M., Intramuscularly

by an adequately-equipped expert—an indication that the wound has not been thoroughly cleaned.

In this account of preliminary experiences in applying penicillin to the treatment of brain wounds it will be convenient to consider the

BRAIN INJURIES

OLOGICAL FINDINGS					RESULTS						REMARKS
Days after Operation					*Healing*				*Late Result*		
2–4	5–7	8–10	11–14	15+	First Intent.	With Sinus and Gape	With Fungus	Abscess	Died	Last Report (Days Post-operative)	
—	*Ps. pyocyanea* *E. coli*	*E. coli* *Staph. aureus*	—	*Ps. pyocyanea* (25)		+				75	Wound involved mastoid
B. aerogenes	—	—	—	—		+				171	
—	—	*Staph. albus* *Ps. pyocyanea*	—	—		+				240	Serous fluid from pinpoint opening on 10th day
E. coli Enterococci	Sterile	*Ps. pyocyanea*	*E. coli*	*E. coli* (20)		+				101	Compound fracture of tibia and gangrenous cellulitis of leg
Ps. pyocyanea	—	—	*Ps. pyocyanea*	—		+				60	
Sterile	—	—	—	—		+				153	
—	*Proteus*	*E. coli*	*Ps. pyocyanea* *E. coli*	—		+				91	
Coliforms	*Ps. pyocyanea*	*Staph. aureus*	—	—		+				171	
Coliforms	—	—	—	—	+					*Ca.* 300	
—	—	—	—	—	+					159	
Staph. aureus *E. coli*	*E. coli*	—	*Ps. pyocyanea* *E. coli*	*Staph. aureus* (18)		+				89	Head wound open to ext. auditory meatus
Ps. pyocyanea	—	—	—	—	+					*Ca.* 300	
E. coli	—	—	—	—					+	7	P.M. Large intracerebral clot
E. coli	—	Sterile	—	—	+					240	
Staph. albus Enterococci	*Ps. pyocyanea* *E. coli*	Sterile	*Staph. aureus* D's	*Staph. aureus* (19)		+				175	‡ Penicillin-resistant *Staph. aureus*
—	*Staph. aureus*‡ *E. coli*	*Ps. pyocyanea* *Staph. aureus*	—	*Staph. aureus* (16)		+				40	Wounds open to nasal passages. P.-o.-W.
—	—	—	—	—				+§	+	2	§ Abscess present before penicillin treatment. P.M. Cerebral œdema
Ps. pyocyanea	—	*E . coli*	—	—				+	+	10	Compound fracture of femur, etc. P.M. Rt. frontal abscess
Ps. pyocyanea	*Ps. pyocyanea* *E. coli* Enterococci	—	—	—	+					81	
E. coli Enterococci	—	—	—	—	+					255	
Ps. pyocyanea	—	—	—	*Staph. aureus* (15) *E. coli*			+	+		170	Compound fracture of Lt. elbow, etc. Brain abscess (*Staph. aureus*) evac. 2 months after wound excision
Ps. pyocyanea	*Ps. pyocyanea*	*Staph. aureus* *E. coli*	*Staph. aureus* *E. coli*	—		+				67	
—	*Ps. pyocyanea* *Proteus*	*Ps. pyocyanea* *Proteus*	—	*Staph. aureus* (15)		+				76	

*, Systemic penicillin for associated compound fracture of long bone
Staph. †, Staphylococcus in a fluid medium and not isolated.
Non-Hæm. Strep., Non-hæmolytic streptococcus
D's, Diphtheroids

following groups: (1) Local application; (2) Systemic treatment; (3) Injections into the cerebrospinal pathways; (4) Injections into the subdural space.

1. LOCAL APPLICATION

a. **Repeated Instillations of Penicillin Solution.**—This method was used in 23 brain wounds 3 to 12 days old during the Sicilian campaign (Cairns, Eden, and Shoreston, 1943). After the wound had been thoroughly cleaned a fine rubber tube was passed through a stab hole into the brain cavity and the wound was closed in two layers; plastic procedures were often necessary to avoid undue tension of the suture line over the dural defect because many of the wounds had already been excised elsewhere. Through the tube penicillin solution (250 units per c.c.) was instilled at the end of operation and subsequently, after preliminary aspiration, at 8- or 12-hourly intervals for 3 to 7 days. The amount instilled varied between 2 and 12 c.c., depending on the size of the cavity. The total dosage was between 2250 and 40,000 units per case (average 15,000 units). Intramuscular penicillin was also given to three of the patients who had compound fractures of limbs.

Of the 23 wounds treated by this method 13 were purulent to the naked eye, and in 4 a brain fungus was presenting in the wound. Nineteen of the 22 examined bacteriologically by Major Scott Thomson contained Gram-positive pyogens.

The clinical and bacteriological course of these cases is set out in *Table I.* One patient (*Case* 17) died from spreading encephalitis 2 days after operation, at which three separate pneumococcal abscesses were encountered in the brain wound. At the time of death he had received only 15,000 units of penicillin locally, an inadequate amount for such an intense and loculated infection.*

Of the remaining 22 cases 2 subsequently developed an abscess in the brain wound, one (*Case* 18) within a few days of operation* and the other (*Case* 21) two months later; both of these had received systemic, as well as local, penicillin. All cases were followed for from two to ten months after operation, and there were no other instances of intracranial infection. The wounds were old and, for the most part, heavily infected and suppurating, and although the series is small it compares favourably as regards the incidence of post-operative infections with previous series (Cairns, 1944).

With this method of repeated instillation of penicillin solution, only 6 of the wounds healed by first intention. In 14 cases a small sinus formed, usually at the point of greatest tension, and discharged pus for some days, then healing in a linear manner. In only one of these cases was the gap sufficiently large to reveal a brain fungus.

Bacteriologically the behaviour of the wounds during treatment could be watched by examination of the aspirated material or discharge from a wound sinus. Before each instillation of penicillin aspiration was performed and as much as 25 c.c. of thin, salmon-pink pus were obtained. The results are set out in *Table I.* Usually, after two days' treatment of the brain cavity with penicillin, Gram-positive cocci were no longer found. Gram-negative organisms of the coliform group—*Ps. pyocyanea*, *Proteus*, and *E. coli*—were almost invariably present, and the questions were raised whether these were introduced into the wound through the tubes, and whether their presence was harmful. In one-half of the wounds Major Scott Thomson had shown that coliform organisms were present before any penicillin treatment was begun. In the others it is possible that coliform organisms may have spread in along the tubes from the skin, or may have been introduced with the solution, but it is equally possible that the organisms may have been already present in some part of the wound before treatment was begun, for bacteriological examination of the wounds at operation was necessarily incomplete (Thomson, 1944). In any event, apart from *Case* 18 there is no evidence that harm resulted from the presence of Gram-negative organisms. In practically all of these brain wounds there was free discharge of Gram-negative pus through the tubes or through wound sinuses during healing, but there was no meningitis, no ventriculitis, no evidence of an advancing lesion due to coliform organisms at any time subsequently, even in cases observed for as long as ten months. *Case* 18 developed, a few days after operation, an abscess containing *E. coli*, and in its wall Gram-positive cocci; in this case there was very little local treatment with penicillin, the débridement is known to have been incomplete, since bone chips were left behind, and it is possible that this abscess may have already been present at the time of operation. Final decision on the importance of Gram-negative pus must await further experience, but the evidence to date is that it is harmless in brain wounds provided it has free exit from the wound. Interference with healing of the scalp is limited to small sinuses which close within a few days, and no case of post-operative brain fungus has followed discharge of Gram-negative pus. However, organisms of the coliform group are not necessarily harmless in the cerebrospinal pathways, and if the pus were to leak into the ventricle severe consequences might arise.

After instillation of penicillin had ceased *Staph. aureus* reappeared in the discharge from the wound in 8 cases. In some cases this could be explained by the fact that the wound was not really a closed wound, but was subject to re-infection from the surface: one involving the mastoid process, for example, was connected with the middle and external ear; another, a bifrontal wound, was connected with the accessory

* The details of this case have been reported elsewhere (Cairns, Eden, and Shoreston, 1943).

nasal sinuses, and in the early days after operation penicillin instilled into the brain cavity at times escaped into the nose. There were 6 cases of wounds on the vertex in which *Staph. aureus* reappeared in the discharges from the drainage hole or a wound sinus between the 5th and 25th day. It seems probable that these cases are examples of persistent infection. In pre-penicillin days these 6 patients would have been likely candidates for a brain abscess, but only one of them subsequently developed it (*Case* 21). The remainder, including one (*Case* 15) with a penicillin-resistant *Staph. aureus*, remained well, with healed wounds for 2 to 10 months.

The provisional conclusion on these old wounds from Sicily was that the incidence of brain abscess had been lower than would have been expected by previous methods, but that the method was capable of improvement. In the later cases of the series the amounts of fluid injected were substantially reduced.

b. **Single Application of Powder.**—In the Italian campaign penicillin was applied as a single application of powder (5000 units of penicillin per gramme of sulphathiazole), after excision of the brain wound. The neurosurgical units were operating on most cases within 24–48 hours of wounding, but, according to Major H. V. Slemon, the wounds were dirtier than those seen in previous campaigns. Frank pus was often present within 24 hours of wounding. When the wound was particularly dirty or moist, it was left open, after application of penicillin powder, for delayed primary suture at the Base. With increasing experience, however, Major Slemon reported that there were few wounds which could not be closed immediately.

Table II.—Local Chemotherapy in Primarily Sutured Penetrating Wounds of the Brain

Local Application	Total	First-intention Healing	Infection	Deaths	Deaths from Infection
Major Slemon's Series.—					
Penicillin-sulphathiazole (5000 u./g.	51	41	3	7	1
Sulphathiazole *	20	10	2	7	2
Major Shoreston's Series.—					
Penicillin-sulphathiazole (5000 u./g.)	78	—	7	—	1
Sulphathiazole	76	—	22	—	6

Sulphadiazine by mouth or systemic injection was given to all patients, an initial dose of 6 g. intravenously followed by 3 g. 6-hourly by mouth.
* One case of this series was not traced.

Working independently, two neurosurgical units in Italy were able to compare the effects of penicillin with those of sulphathiazole as a local application to brain wounds. In each unit at one period penicillin was not available, and during that time wounds were treated with sulphathiazole alone. The results are shown in *Table II*. Major Slemon's cases were mostly operated on within 24 hours of wounding. Major Shoreston's sulphathiazole series included a group of 11 cases in which the wounds were more than 3 days old; in his penicillin series most cases were treated with a single application of powder, but penicillin solution was employed when it appeared that the powder would not reach all parts of the track or when the wound was already purulent. Of necessity, Major Shoreston's and Major Slemon's cases have not been followed for more than two months, but as far as they go they indicate a diminution of sepsis as the result of local application of penicillin. In the penicillin-treated cases a death-rate from infection of 1 in 51 cases in Slemon's series and 1 in 78 cases in Shoreston's series probably represents a new low level for deaths from sepsis in brain wounds. It is to be noted that in both series sulphadiazine was given to all cases by mouth or systemic injection; this point will be discussed later.

2. SYSTEMIC PENICILLIN

The value of systemic penicillin in the treatment of brain wounds has not yet been precisely established. In the early work shortage of supplies prompted the development of local treatment, but during the Sicilian campaign three patients with brain wounds were treated systemically as well as locally because they also had compound fractures of long bones. Two of these patients subsequently developed a brain abscess (Cairns, Eden, and Shoreston, 1943).

When larger amounts of penicillin became available we supplemented local with systemic penicillin in an increasing number of cases. It has proved particularly valuable in those cases of brain wound in which the scalp part of the wound is swollen and purulent. These are often cases in which an incomplete débridement has already been carried out and infection has thus gained access to the subgaleal plane. With systemic treatment for 48 hours the swelling subsides and the wound can be safely sutured.

Wholesale treatment of all brain wounds by the systemic route is not advocated at present. Systemic penicillin does not prevent brain abscess, in the absence of thorough surgical toilet of the wound. On the other hand, it has a remarkably beneficial, and often a crucially important, effect in those cases in which there is pyogenic infection of the overlying scalp. Its use is also indicated in those not infrequent cases in which a brain wound is associated with septic wounds of the limbs or trunk.

3. INJECTIONS INTO CEREBRO-SPINAL PATHWAYS

Experience in the treatment of meningitis and ventriculitis with penicillin (Cairns, Duthie, Lewin, and Smith, 1944) has shown that when a dose of 4000 to 10,000 units is injected into the

lumbar subarachnoid space or the lateral ventricle it spreads, in the absence of block, to all parts of the cerebrospinal pathways; and in most subjects it persists in the cerebrospinal fluid at a level above that required for complete bacteriostasis for about 24 hours. The need for the strictest asepsis during preparation, injection, and storage of solutions, in order to avoid introducing insusceptible Gram-negative organisms, has already been stressed.

Ventriculitis and meningitis may arise primarily after transventricular wounds, or penetrating wounds involving the accessory nasal sinuses or ear. More often infection of the cerebrospinal pathways is secondary to an abscess in the track of the brain wound. While primary pyogenic meningitis can be satisfactorily overcome by regular daily intrathecal injections of penicillin, this method of treatment by itself is useless when the meningitis is secondary to a brain abscess or other suppurating focus. For example, in a case of infected brain wound discharging into the ventricle and associated with meningitis it is useless to inject penicillin into the cerebrospinal pathways without treating the brain wound surgically. The cerebrospinal fluid quickly becomes sterile, but the patient dies unless the focus of suppuration is operated on.

In the treatment of meningitis with intrathecal injections of penicillin, it must be emphasized, an adequate concentration of penicillin must be *maintained* in the cerebrospinal fluid until the clinical signs of the meningitis have cleared up and the cellular content of the cerebrospinal fluid has fallen. Experience with penicillin in pneumococcal meningitis has shown that if this precaution is neglected the meningitis may suddenly flare up, with the development of a block in the subarachnoid space or aqueduct of Sylvius, a complication which may render further injections of penicillin ineffective. Thus, regular daily injections of penicillin are required, and if the case is not progressing satisfactorily the penicillin content of the cerebrospinal fluid from the ventricle and the lumbar region should be assayed 24 hours after injection to ascertain whether penicillin is diffusing freely to all parts, and whether an adequate concentration is being maintained.

PROPHYLACTIC USE OF INTRATHECAL PENICILLIN

a. **Recent Ventricular or Paraventricular Wounds.** — Ventricular and paraventricular wounds have always carried a high mortality and often the resulting ventricular infection is not controlled by sulphonamides. Recently in Italy Captain F. J. Gillingham has applied penicillin in the treatment of this problem.

A male, aged 30, was injured by shell fragments in the left parietal region on April 22, 1944, He came under Captain Gillingham's care on May 8, 17 days after injury. He was alert, but spoke only in monosyllables. There was a tiny scabbed wound in the left parietal region. X rays showed a small defect in the left parietal bone, a shower of bone chips 3 cm. deep in the left parietal lobe, and a fragment of metal 7 cm. deep, which appeared to be in the left lateral ventricle, but did not move with changes of the position of his head. There were papilloedema, probably right homonymous hemianopia, and severe sensory and motor paralysis affecting the right side of his body. The signs were gross for such a small wound 17 days old, and it was thought that there might be a large blood-clot deep in the right hemisphere. Operation was decided on and before it was done penicillin solution was injected into the lumbar theca (3750 units) and into the left lateral ventricle (3750 units). Lumbar cerebrospinal fluid: pressure 200 mm., total protein 90 mg. per cent, white cells 110 per c.mm., culture sterile. Ventricular cerebrospinal fluid: hazy fluid, total protein 90 mg. per cent, red cells 2680, and white cells 8 per c.mm., culture sterile.

On May 8 Captain Gillingham explored the left parietal wound. The tear in the dura (2·0 cm. by 1·5 cm.) was closed by blood-clot and bone fragments. When these were removed by suction liquefied blood-clot welled out under pressure, and 20 chips of bone (culture, *Staph. aureus*) were removed. After all the blood-clot had been sucked away there was a huge cavity (7 cm. × 5 cm. × 5 cm.) with a yellowish wall covered here and there by dirty brown patches. At the bottom of the cavity there was a small ball of débris which proved to contain the metal foreign body, embedded in the wall of the lateral ventricle. When it was removed there was a gush of cerebrospinal fluid. The dural opening was closed with a free graft of pericranium, and before the last suture was tied penicillin solution (3750 units) was injected into the cavity and the wound was frosted with penicillin-sulphathiazole powder. The wound was closed without drainage.

On the following day lumbar and ventricular punctures were done; there was considerable increase in the protein and cellular content of the ventricular fluid, but cultures were sterile. Penicillin solution (3750 units) was again injected into the ventricle. This was repeated on the next day, May 10, when the protein and cellular content of the ventricular fluid had fallen. The patient made a quick recovery. On June 12 his lumbar cerebrospinal fluid contained 40 mg. per cent of protein and less than 1 white cell per c.mm., and culture was sterile. Air encephalography on the same day showed a diverticulum where the clot had been, connected with the left lateral ventricle by a narrow channel. The patient had some residual spastic weakness and sensory loss of the right arm and leg. His visual fields were full and his optic discs were flat.

This is a good example of the prophylactic use of penicillin in a case in which the cerebrospinal pathways were inevitably contaminated during removal of a paraventricular blood-clot and bone chips harbouring *Staph. aureus*. While there would appear to be little doubt of its value in such cases, it is difficult to compare this with previous experience, because hitherto the attitude of the neurosurgeon towards para- and transventricular wounds has been less aggressive than it now appears likely to become, with the prospect of being able to prevent secondary meningitis with Gram-positive organisms by means of penicillin.

b. **Chronic Brain Abscess.**—Penicillin has been similarly used when the ventricle has been opened and contaminated during removal of a chronic staphylococcal brain abscess after a gunshot wound.

c. **Cerebrospinal Fistula.**—Penicillin can also be used prophylactically by intrathecal lumbar injection before closure of a cerebrospinal fistula following incomplete healing of a wound of the vertex, or wounds of the cranial base involving the ear or accessory nasal sinuses.

4. INJECTIONS INTO THE SUBDURAL SPACE

In chronic suppuration after brain wounds the subdural space only occasionally becomes infected. From some observations which I have recently made with Drs. E. S. Duthie and Honor Smith it appears that penicillin in the subdural space disappears much more quickly than in the subarachnoid space. Consequently, subdural space infections are best treated by indwelling tube and frequent injections of penicillin. In one case of diffuse purulent pachymeningitis of the left hemisphere a successful outcome followed injections of penicillin at 3-hourly intervals.

EARLY BRAIN ABSCESS

Brain abscess in the first weeks after wounding is treated by local drainage and removal of any indriven bone fragments which still remain. A brain fungus is almost invariably present. Provided the whole of the abscess cavity is drained, these cases usually do well. The process of sterilization can be assisted by passing a fine rubber tube to the bottom of the abscess cavity and instilling penicillin solution (1000 units per c.c.) into the cavity twice a day for 3 to 5 days, each instillation being preceded by aspiration. Gram-positive cocci quickly disappear from the discharge. Gram-negative organisms, such as *Ps. pyocyanea*, sometimes appear in the discharge, but so far have not caused any trouble.

SULPHONAMIDES SYSTEMICALLY AS AN ACCESSORY METHOD OF TREATMENT

Although in the first cases of head wounds treated with penicillin no sulphonamides were given systemically, it is now recommended in all cases of intracranial infection after gunshot wound that the patient should receive sulphadiazine or sulphamezathine by mouth or intravenous injection, as well as penicillin. The object is to prevent or check the development of meningitis. Experience in North Africa favoured this course (Eden, 1943) and our policy was determined by our experiences with pneumococcal meningitis (Cairns, Duthie, Lewin, and Smith, 1944), which provided convincing evidence that regularly-administered sulphonamides could hold the infection in check, at least for a time. This effect was often striking in the initial stage of cases which without the aid of penicillin would subsequently have died.

It is easy to establish and maintain an adequate level of sulphadiazine or sulphamezathine in the cerebrospinal fluid by oral or intravenous administration. To obtain the same result with penicillin it is necessary to inject penicillin into the cerebrospinal pathways under strict aseptic precautions at not less than 24-hour intervals, with unfailing regularity, and this is often impracticable in the treatment of battle casualties. Therefore, though sulphonamides are much less effective than penicillin in meningitis, as has been demonstrated in the treatment of pneumococcal meningitis, the ease with which they can be administered and can pass through the blood-cerebrospinal fluid barrier renders them useful as an accessory chemotherapeutic agent in the treatment of brain infections.

NON-PENETRATING HEAD WOUNDS

Penicillin was used in the treatment of non-penetrating head wounds during the battle of Sicily when wounds up to 18 days old and for the most part suppurating, which previously would have been left to granulate, were included among those sutured (Cairns, Eden, and Shoreston, 1943). Two methods were tried. In one a tube was inserted through a stab drain and the wound was closed after excision; penicillin solution (250 units per c.c.) was injected twice daily for 3–5 days. Though the end-result was satisfactory and there was never any exacerbation of pre-existing infection as a result of closure, a small sinus usually formed in some part of the wound and discharged pus for some days before it finally healed.

In the other method, which was less time-consuming, wounds were treated with a single application of penicillin-sulphanilamide powder (1000 units per gramme) at the time of suture. The results were better than with the first method. There were 2 failures in 12 wounds. One of these was doubtless due to the fact that in an 11-day-old wound the scalp was closed over bare and probably infected bone. In the other case failure was unexpected, because, though the wound was infected with *Staph. aureus*, it was only 4 days old and there was no fracture of the skull. It was probable that in this case bleeding during closure washed most of the powder out of the wound. After this experience scalp vessels were sealed by endothermy before closure and more powder was insufflated before the last galeal stitch was tied.

More experience in Italy has shown that wound closure with a single application of penicillin-sulphathiazole powder (5000 units per gramme) resulted in healing by first intention in 95 per cent of cases, and the results were considerably better than when, owing to absence of penicillin, sulphanilamide-proflavine powder was substituted (*Table III*).

However used locally, penicillin is not effective in promoting primary healing of gunshot wounds which are closed over a damaged skull. In skull wounds treated after closure with repeated injections of penicillin solution through tubes, the material discharged or aspirated from the wound has sometimes yielded penicillin-sensitive Gram-positive cocci during and after 5 days' treatment with penicillin. Penicillin is so certain in its effects that this phenomenon can only be explained by loculated infection in the bone, to which penicillin had no access. The indications are that a wide excision of the damaged area of the skull is necessary before closure of the wound.

Table III.—PRIMARY CLOSURE OF NON-PENETRATING HEAD INJURIES

	Skull Fractured		Scalp Wound Only		Total	Infected
	No. of Cases	Infected	No. of Cases	Infected		
With penicillin-sulphathiazole powder	73	9	151	2	224	11
With sulphanilamide-proflavine powder	21	7	106	8	127	15

This table was prepared by Captain G. K. Tutton from the records of a neurosurgical unit (O.C., Major J. Shoreston). The wounds of the penicillin-sulphathiazole series were slightly older than those of the sulphanilamide-proflavine series, but the majority of wounds in both groups were less than 72 hours old at the time of suture.

SPINAL CORD INJURIES

In spinal injuries penicillin may be useful as a prophylactic against meningitis. In the Sicilian campaign two back wounds were treated in which the missile penetrated the spinal canal.

In the first of these there was a cerebrospinal fluid leak through a wound infected with *Staph. aureus* and *Proteus*. During a course of intramuscular penicillin this wound was excised and closed in layers. The leak ceased and the wound healed, partly by granulation, without any signs of meningitis.

In the second case a fragment of mortar bomb lodged in the cauda equina. On the second day the wound was excised in the Forward Area, treated with penicillin and sulphanilamide powder (5000 units of penicillin per gramme) and left open. On the seventh day at Tripoli the wound, which looked clean, was closed with four layers of stitches after a further application of penicillin-sulphanilamide powder. Unfortunately no cultures were taken. Fifteen days later this wound appeared perfectly healed, and the patient had had a smooth convalescence.

SUMMARY

1. Although the methods of using it are as yet far from standardized, penicillin has proved a most useful substance in the prevention and treatment of infection associated with gunshot wounds of the head; but, however it is applied, it will not be effective unless the dirt, hairs, bone chips, pulped brain, blood-clot, etc., and such missiles as are easily accessible are first removed by surgical excision.

2. In recent brain wounds (up to 72 hours old) calcium penicillin can be applied as a powder (5000 units of penicillin per gramme of one of the sulphonamides) followed by primary closure. In 129 cases so treated fatal infection developed in only 2 cases.

3. In older brain wounds where pus is already present, penicillin can be applied as follows:—

a. After excision and primary closure of the wound sodium or calcium penicillin solution (250 to 1000 units per c.c.) can be instilled through tubes twice daily for 3–5 days. Of 23 old brain wounds so treated only 3 subsequently showed major intracranial infection.

b. The wound can be cleaned surgically and left open for 2–3 days with once- or twice-daily application of penicillin powder; secondary suture can then be performed.

c. If at operation the scalp is found to be grossly infected the whole wound is surgically excised in the usual way, the scalp is partially closed, and a 2–3-day course of systemic penicillin is given.

4. In ventricular or paraventricular wounds where there is overt or potential ventriculitis, penicillin solution (1000 units per c.c.) should be injected into the ventricle or lumbar theca in amounts of 4000 to 8000 units once daily for as long as there is any suspicion of ventricular infection. This treatment is useless unless the source of infection is also dealt with by surgical toilet of the wound.

5. Abscess arising in a brain wound within the first few weeks after injury should be treated by open drainage, removal of accessible bone chips, and twice- or thrice-daily instillations of penicillin solution through an indwelling tube.

6. A single injection of penicillin, 4000 to 8000 units, should be given into the lateral ventricle or lumbar theca as a prophylactic agent against meningitis immediately before operation for the following conditions: (*a*) removal of a chronic brain abscess; (*b*) closure of a cerebrospinal fistula; (*c*) repair of the dura after orbitofrontal or naso-frontal wounds, or wounds involving the petrous temporal bone.

7. In all injections of penicillin solution into the cerebrospinal pathways the solution should be passed through a Seitz filter and full aseptic precautions must be taken to avoid contamination of the meninges with such penicillin-resistant organisms as *E. coli*, *Ps. pyocyanea*, and *Proteus*.

8. Sulphadiazine or sulphamezathine is a useful additional agent in the prevention and treatment of meningitis due to susceptible organisms, and should be administered by mouth or intravenously, with the usual precautions, in all head wounds in which there is risk of infection of the cerebrospinal pathways.

9. Closure of non-penetrating gunshot wounds of the head after excision (including thorough removal of bare bone) and insufflation of penicillin powder is followed by primary healing in 95 per cent of cases. Careful hæmostasis is required before closure to prevent the powder being washed away by the blood. The results have been shown to be superior to those obtained with the aid of sulphanilamide-proflavine powder.

10. Causes of failure to overcome the infection of head wounds with the aid of penicillin include the following: (*a*) lack of proper access, owing to inaccessible or imperfectly excised loci of infection; (*b*) inadequate treatment both in amount and duration; (*c*) washing away of penicillin by blood before the wound is closed; (*d*) undetected deterioration in the preparation of penicillin used.

11. Penicillin can be used to prevent meningitis resulting from the closure of open wounds of the spinal canal.

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OBSERVATIONS ON THE PROPHYLACTIC USE OF PENICILLIN IN THE WOUNDS OF AERIAL WARFARE

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THE following is a report on the use of penicillin as a prophylaxis for infection in wounds sustained in aerial combat. This study has been carried out under the direction of the Office of the Chief Surgeon of the European Theatre of Operations and is based on observations made in seven U.S. Army Hospitals serving the U.S. Army Air Forces, European Theatre of Operations.

We are indebted to the Commanding Officers, the Chiefs of the Surgical Services, the Chiefs of Laboratory, and their staffs, in each of the participating hospitals for every consideration in the management of cases, the performance of laboratory procedures, and the recording of data, and we wish to acknowledge our gratitude to Brig.-General Malcolm C. Grow, M.C., Surgeon, U.S.S.T.A.F., and the Surgeon of the U.S. Army Air Forces, E.T.O., without whose full co-operation and assistance this study would have been impossible.

It should be clearly understood that the object of this study is not to determine whether penicillin is effective in established wound infections, but rather to learn whether penicillin, used prophylactically, will prevent or lower the incidence of infection in the wounds of aerial combat in a theatre of war where early definitive surgery and continued observation can be carried out.

PLAN FOR STUDY

The wounded patients were divided into two groups. Those in one group were given parenteral and local penicillin prophylactically in a manner to be described. Those in the other group received no chemotherapeutic agent and serve as controls. A further control already existed in the study made by Lieut.-Colonel MacFee on wounded airmen in whom sulphonamides had been administered both prophylactically and therapeutically.

Every patient in each group was managed in accordance with well-established surgical principles. First aid was given in the plane shortly following injury and usually consisted of sterile dressings and sedatives as well as tourniquets where necessary. Upon arrival at the air field the patient received treatment for shock, his wounds were dressed and splinted, and as soon as his condition permitted he was transported to the hospital. Pre-operative preparation at the hospital consisted in continuation of shock therapy, when necessary, and sedation, X rays, and examination. On an average the airman was ready for operation within six hours after being wounded. The shortest interval was four and the longest thirteen hours.

At operation the wound was débrided as thoroughly as possible without the sacrifice of vital structures, and irrigated with physiological saline solution. Fractures were immobilized in plaster or by skeletal traction. Primary closure of the wound was carried out in one-third of the compound fracture cases and in two-thirds of the wounds involving only the soft parts. The remainder of the wounds were left open. Many of the latter were subsequently closed by early secondary suture or early skin-grafting. At no time, in plane, at field, or in hospital did any of these patients receive, prophylactically, any chemotherapeutic agent other than penicillin.

Penetrating wounds of the abdomen or thorax or burns are not included in this study. The policy has been to administer sulphonamides or penicillin or both to all such patients, therefore no group of control cases is available for comparison.

ADMINISTRATION OF PENICILLIN

Every patient in the penicillin group received local and parenteral penicillin. The local dosage for wounds involving only soft tissue varied from 5000 to 20,000 units in accordance with the size of the wound. Wounds associated with compound fracture and soft-part wounds in the region of the anus or buttocks received from 10,000 to 40,000 units. In a limited number of instances doses as great as 100,000 units were administered. This has been the exception rather than the rule.

The usual method of preparation for local application has been to dissolve the sodium salt of penicillin in sterile physiological saline solution in amounts of 1000 units of penicillin per cubic centimetre. This solution was sprayed on the wound by means of an atomizer. Another method only recently developed has been the insufflation of a mixture of penicillin powder and dehydrated human plasma on the wound surface. Ten thousand to 20,000 units of the sodium salt of penicillin to 0·1 to 0·2 g. of plasma has been found to be a satisfactory combination. Experience with the plasma method of local penicillin therapy in one of the units has demonstrated its superiority over previously employed methods. However, the preparation of the mixture as described in hospitals is time-consuming and not practical for general use. We have suggested that such a combination should be prepared in advance and delivered to hospital units with penicillin already mixed with dried plasma in suitable amounts for use in wounds.*

The local use of penicillin was combined with parenteral administration. The practice was to give intramuscularly 10,000 units of the sodium salt dissolved in 1 c.c. of physiological saline solution. This dosage was given immediately following operation and was repeated at three-hour intervals. Early in the study parenteral administration was continued for three days, but subsequently this was reduced to 48 hours. In a few cases an intramuscular dose of 20,000 units dissolved in 1 c.c. of saline solution was given, and in a few instances prophylactic administration was continued beyond the three-day period.

The series was remarkably free from unfavourable reactions which could be attributed to the use of penicillin. Burning pain at the site of injection occurred in many instances.

Table I.

	Penicillin Group		Control Group	
	Number	Infection	Number	Infection
Compound Fractures :—				
Scapula :				
Wound closed per primam	1	0	1	0
Wound left open	3	1	1	0
Humerus :				
Wound closed per primam	2	0	2	0
Wound left open	4	0	1	0
Radius and ulna :				
Wound closed per primam	1	0	2	0
Wound left open	7	0	2	1
Carpals and phalanges :				
Wound closed per primam	0	0	2	0
Wound left open	2	0	1	1
Femur :				
Wound closed per primam	1	0	4	1
Wound left open	6	2	1	0
Tibia and fibula :				
Wound closed per primam	0	0	1	1
Wound left open	7	3	4	0
Tarsals and phalanges :				
Wound closed per primam	0	0	2	0
Wound left open	1	0	4	1
Sacrum, ribs, maxilla :				
Wound closed per primam	1	0	0	0
Wound left open	2	0	0	0
Soft-part Wounds :—				
Head, face, and neck :				
Wound closed per primam	8	0	7	0
Wound left open	0	0	0	0
Trunk and thoracic wall :				
Wound closed per primam	7	0	3	0
Wound left open	3	2	1	0
Upper extremity :				
Wound closed per primam	24	0	25	0
Wound left open	7	0	11	1
Lower extremity and buttock :				
Wound closed per primam	20	2	28	2
Wound left open	16	1	24	3

RESULTS

This study is based on 250 wounds occurring in 146 patients. Sixty-eight patients with 123 wounds are in the penicillin group; 78 patients with 127 wounds are in the control group.

The results have been judged solely from the standpoint of wound infection. The criteria for infection required the presence of one or more clinical signs such as tenderness, swelling, redness, lymphangitis, lymphadenitis, the presence of purulent discharge or infected hæmatoma. In wounds which were left open a distinction has been made between those having simple surface contamination and those showing clinical infection. The presence of organisms on the surface

* Recently, through the courtesy of the Medical Research Council Drying Unit (British), penicillin has been dried with each of the following materials—human plasma, albumin, and globulin in known quantity and dosage. Preliminary tests have shown the various combinations to be sterile and the penicillin potent. The clinical results with these new combinations have been limited, but there is indication that the method has many advantages and gives promise of an effective and convenient method for local application of the drug.

of an otherwise healthy wound is not considered infection of that wound.

For the purpose of presenting the data obtained in this study and in recognition of differences in wounds and their management, certain groupings of these wounds are necessary. The compound fractures have been separated from wounds involving only the soft parts. The former have been grouped on the basis of the bone involved, the latter on the basis of anatomical location. Further division into wounds closed *per primam* and wounds left open has been made. The number of wounds and the number of wound infections in each group is indicated in *Table I*. The results from the standpoint of the incidence of wound infection are given in the self-explanatory *Tables II–IV*.

Table II.—Infection Rate with Respect to Wounds in Patients Receiving Penicillin Prophylactically Compared with those Receiving no Chemotherapeutic Agent

	Number of Patients	*Number of Wounds*	*Wound Infection*	*Inspection Rate with Respect to Wounds*
Total	146	250	22	8·8 per cent
Penicillin group	68	123	11	8·9 „ „
Control group	78	127	11	8·7 „ „

Table III.—Infection Rate in Compound Fractures (Exclusive of Skull Fractures) Receiving Penicillin Prophylactically compared with those Receiving no Chemotherapeutic Agent

	Number	*Infections*	*Infection Rate*
Total	66	11	16·7 per cent
Penicillin group	38	6	15·8 „ „
Control group	28	5	17·9 „ „

Table IV.—Infection Rate in Soft-part Wounds Receiving Penicillin Prophylactically Compared with those Receiving no Chemotherapeutic Agent

	Number	*Infections*	*Infection Rate*
Total	184	11	6·0 per cent
Penicillin group	85	5	5·9 „ „
Control group	99	6	6·1 „ „

Nineteen patients developed infection in 22 wounds. Three of these infections were cases of gas gangrene. Each had a compound fracture associated with considerable comminution of bone as well as maceration of muscle and other soft parts. All had bled extensively and arrived at the hospital in profound shock. Following infusions of plasma and transfusion of blood, recovery was sufficient in each instance to permit what at the time seemed to be satisfactory surgical treatment of the wounds.

In two cases the wounds were débrided, irrigated, and left open. Penicillin was used locally and parenterally. The third case received débridement, irrigation, and closure. No penicillin was used. All three developed clinical gas gangrene. The first two cases recovered; one, following mid-thigh amputation; the other, after excision of the involved muscle group. The third case required mid-thigh amputation and was given antitoxin and penicillin therapeutically. Despite the fact that the local infectious process was completely controlled, death ensued from uræmia. Microscopical examination of the kidneys revealed hæmoglobinuric nephrosis. This was the only fatality in either of the groups of cases.

The remaining infections were of considerably less magnitude than these three described above. All responded promptly to treatment; there were no complications and no prolonged hospitalization because of infection.

Twelve patients with compound fracture of the skull received penicillin. They are not included in any of the tables of this report because there are no compound skull fractures in the control group with which they can be compared. Except for one which involved the frontal sinus, all were instances of dural penetration. Four were associated with multiple bone and soft-tissue injuries of other parts. Eleven received parenteral and local penicillin, while one was given the drug parenterally only. The entire group received early and thorough neurosurgical management. There was one infection, a superficial, localized brain abscess from which hæmolytic coagulase-positive staphylococci were cultured. Recovery following drainage of the abscess was prompt.

Not included in any of the tables of this report are 20 wounds occurring in 14 patients who were not given penicillin parenterally. The wounds, however, received at the time of débridement single local applications of penicillin in doses from 5000 to 20,000 units. In this group there were 19 soft-part wounds, 15 closed *per primam*, and 4 left open, and 1 compound fracture, left open. One wound, involving the soft tissue of the posterior thigh, which received 5000 units of penicillin and which was closed with slight tension, became infected. The remaining wounds healed without complication.

BACTERIOLOGICAL FINDINGS

An effort was made to obtain as much pertinent laboratory data as possible. At the time of operation the débrided tissue from the majority of the wounds was placed in sterile wide-mouthed bottles and saved for culture. Following débridement and irrigation the wound was again sampled for bacteriological examination. This was done by gently and thoroughly passing, over all parts of the wound, a sterile cotton swab, which was later cultured. In the beginning of the study only aerobic cultures were done. Later, four of the hospitals had facilities for anaerobic, as well as aerobic, cultural methods.

Cultures were obtained from 165 of the 250 wounds reported; 141, or 85 per cent, showed bacterial growth. The predominant organism was the staphylococcus, isolated 97 times. Other organisms and the number of times each was isolated are as follows: streptococci, 15; diphtheroids, 15; Gram-positive cocci, 9; Gram-negative bacilli, 16; Gram-positive bacilli, 13; anaerobic Gram-positive bacilli, 24; other anaerobic organisms, 6; other organisms, 6.

The staphylococci from 42 separate wounds were tested for sensitivity to penicillin. In 36 instances the organisms were found to be sensitive; the remaining 6 (or 14 per cent) were penicillin-resistant.

It is interesting to note that among the wounds showing growth of organisms in the débrided tissue only 29 per cent became free from bacteria, as determined by cultures, following débridement. In other words, despite débridement and irrigation, almost three-fourths of the wounds remained contaminated. By this we do not mean to infer that quantitative reduction of the wound flora is not accomplished by surgical methods.

Cultures were obtained from 16 out of the 22 infected wounds. Anaerobic Gram-positive bacilli, having subterminal spores and producing stormy fermentation in iron milk, were cultured from each case of gas gangrene. One was identified as *Cl. welchii*, the other two were members of the clostridial group, presumptively *Cl. welchii*. The purulent exudate of another infected wound, not gas gangrene, yielded a pure culture of *Cl. welchii*. Another wound, a superficial one, had on its surface a mixture of Gram-negative bacilli, Gram-positive cocci, and clostridia. Hæmolytic streptococci, in pure culture, were responsible for the cellulitis of another case. The remaining 10 infections were due to staphylococci.

DISCUSSION

In this study an effort is made to evaluate penicillin as the sole chemotherapeutic agent in the prophylaxis for infection in the wounds of aerial warfare. The findings are presented in the tables. The differences in percentage between the infection rates in the penicillin group and control group in each instance are not of statistical significance.

This report is not a 'questionnaire' study. Over one-half of the cases reported were actually observed at the time of operation and during the post-operative period by one of the authors of this report. Information on the remaining cases was recorded on special forms; however, one of the authors made frequent visits to the hospitals contributing to this study and discussed the cases with the responsible surgeons.

The results indicate that penicillin, used in conjunction with early definitive surgery, did not lower the incidence of infection in such wounds. We cannot too strongly emphasize that our findings are not to be compared nor confused with other studies in which penicillin has been used to treat established surgical infections.

No attempt will be made to draw conclusions from isolated cases. It is, however, obvious that penicillin used prophylactically in the manner herein described did not prevent the development of gas gangrene in two patients. The role of this agent in modifying the infection, altering the toxicity, or in combating secondary invaders, cannot be evaluated at the present time. These two patients who received penicillin prophylactically as well as the one who received it therapeutically had enough penicillin in their blood-serum to produce bacteriostasis of the Florey staphylococcus as late as three hours after the administration of penicillin intramuscularly.

Primary closure carried out 4 to 13 hours after wounding, may appear unwarranted. It is certainly at variance with the belief that all war wounds should be left open. It must be remembered that the cases reported here constitute a special group of war wounds. The patients were aerial combat casualties, injured and remaining after injury in an environment relatively clean compared with that of the ground force. The first aid rendered in the plane by fellow crewmen and the early primary treatment at the airfield, in the form of dressings, splints, sedatives, and plasma, are factors which contribute greatly to a favourable outcome. The patients were transported without delay to the place of definitive surgery. Moreover, continued and frequent observations by the surgeon who closed the wound were assured.

Throughout this study it has been necessary to curtail many desirable bacteriological investigations in favour of a practical laboratory programme. Nevertheless, there are several points of interest from the bacteriological standpoint. One has been the finding of a high percentage of contaminated wounds in aerial casualties. As noted above, the predominant organism has been the staphylococcus. Another contaminant worthy of note is the clostridium. The incidence of this organism in cultures of the débrided tissue increased as improvements were made in the anaerobic methods in the different laboratories. In one of the laboratories, when anaerobic as well as aerobic cultures were done routinely, the incidence of clostridia (anaerobic Gram-positive bacilli) in the débrided tissue was 24 per cent. Equally noteworthy has been the infrequent recovery of streptococci and enterobacilli. Another interesting finding has been the persistence of contaminating organisms in almost three-fourths of the wounds after débridement and irrigation.

SUMMARY

1. A report on the evaluation of penicillin as a prophylaxis for infection in aerial warfare wounds is presented.

2. The prophylactic administration of penicillin is not to be compared nor confused with its therapeutic use in established infections.

3. Penicillin was given, parenterally and locally, to 68 patients having 123 wounds. Another 78 patients having 127 wounds and receiving no chemotherapeutic agent were compared with this group. All patients received early definitive surgery. The rate of wound infection in the penicillin group was 8·9 per cent, that of the control group 8·6 per cent.

4. Compound fractures (exclusive of skull fractures) in which penicillin was used had an infection rate of 15·7 per cent; that of the control group was 17·8 per cent.

5. Wounds involving the soft parts only in which penicillin was used had an infection rate of 5·8 per cent; that for the control group was 6·0 per cent.

6. Cultures of the tissue removed at operation, as well as swabs following débridement and irrigation, indicate that 85 per cent of these wounds are contaminated, and that in 71 per cent of the wounds contamination persists after débridement and irrigation have been completed.

CONCLUSIONS

One group of aerial combat wounds was treated by débridement, followed by the prophylactic use of penicillin. A comparable group received the same surgical treatment, but no penicillin or other chemotherapy. There was no significant difference in the infection rates in the two groups.

By the methods employed, therefore, penicillin does not appear to have reduced the incidence of infection under the conditions present in aerial combat in this theatre of operations where early definitive surgery and continued observation is practicable.

PENICILLIN THERAPY IN GONORRHŒA

A REPORT OF 1000 CASES OF SULPHONAMIDE-RESISTANT GONORRHŒA AND 100 CASES OF ACUTE GONORRHŒA PREVIOUSLY UNTREATED

By JOHN N. ROBINSON, Major, M.C., U.S. Army

This report is based on 1000 cases of sulphonamide-resistant gonorrhœa treated in fifteen U.S. Army Hospitals in the European Theatre of Operations and on 100 cases of acute gonorrhœa. These cases are in addition to those previously reported by the author (1944) who has personally observed 150 of the patients. The data were collected through the Office of the Chief Surgeon, E.T.O.

SULPHONAMIDE-RESISTANT GONORRHŒA

Selection of Cases.—Only patients with gonorrhœa considered sulphonamide-resistant by failure to respond to a ten-day course of sulphatherapy, were selected for penicillin therapy. Those showing signs of sensitivity to any of the sulpha derivatives were accepted earlier than ten days for penicillin treatment. In addition, all cases developing complications, such as epididymitis, prostatitis, or abscess while on chemotherapy, were given penicillin.,

Method and Dosage.—947 cases of gonorrhœa received penicillin intramuscularly in either 10,000-unit doses given every hour or in 20,000-unit doses given every three hours until a total of 100,000 units was reached. In the other 53 cases which did not respond satisfactorily to such dosage, a second course of penicillin was necessary. In this latter group 40 cases received 10,000 units every hour for 10 doses, and 3 received 20,000-unit doses given every three hours for 5 doses, making an additional total of 100,000 units. The remaining cases all had more than 100,000 units, 3 received 130,000 units, and 7 received 150,000 units; 3 cases in the latter group were given 200,000 additional units, 20,000 every 3 hours.

Duration of the Gonorrhœa.—This resistant group of cases had in most instances received many types of treatment, and as a result the disease was of fairly long standing, varying from 1 week to 44 weeks, with the average duration of the gonorrhœa being 4 weeks, before instituting penicillin therapy. However, the length of time before a patient received penicillin has rapidly decreased from the first cases, when it was not readily available, until now, when all cases are routinely sent to the hospitals for penicillin as soon as it is demonstrated that chemotherapy is not successful.

Previous Treatment.—To appreciate more fully how effective penicillin proved, it is only necessary to review the amount and type of treatment received by the first 500 cases observed and to compare them with the last group.

An average of 80 g. per patient of either sulphathiazole or sulphadiazine, or both, was given prior to this therapy. In a few instances sulphapyridine or sulphanilamide was tried. The amounts varied from 10 to 500 g.; 320 (64 per cent) received both sulphadiazine and sulphathiazole; 118 (23·6 per cent) were given sulphathiazole alone, and 62 (12·4 per cent) received only sulphadiazine; 78 (15·3 per cent) had some form of local treatment to the anterior urethra, and 33 (6 per cent) received some type of fever therapy in addition to the sulpha drugs.

In comparison the last 500 cases gave an entirely different picture, which is encouraging. An average of only 40 g. per patient was given before initiating penicillin therapy. The use of sulphathiazole and sulphadiazine was in the same proportion with the exception of the dosage. However, the striking difference was that none of these cases had received local treatments or any type of fever therapy before penicillin.

Laboratory.—It was not possible to perform a complete laboratory study in every case because

of limited facilities in certain of our smaller hospitals. However, the majority of patients had a complete blood-count, and an erythrocyte sedimentation rate was taken in most instances with complications. Smears of the urethral discharge were done on all before treatment was started. If the smear did not show the gonococcus, or proved doubtful, a culture was taken. After completion of the treatment three negative smears and at least two negative cultures, taken at 24-hour intervals, were obtained before the patient was released from hospital. All those with additional prostatic involvement were required to have a negative culture of the prostatic fluid before discharge to duty.

Results of Treatment.—The results were all ultimately satisfactory and can best be discussed by dividing the cases into two groups: (1) those requiring only one course of 100,000 units of penicillin; and (2) those requiring more than one course of therapy.

In the first group 947, or 94·7 per cent (of the cases of sulpha-resistant gonorrhœal urethritis), were treated with 100,000 units of penicillin intramuscularly with successful results; 606 (63·9 per cent) of these cases involved the anterior urethra only, while 341 (36·1 per cent) had disclosed a spread to the posterior urethra as well. Of these 341 cases, 73 had other complications, divided as follows: 40 with acute epididymitis, of which 4 were bilateral; 28 with prostatitis, of which 21 were chronic, 5 were acute, and 2 were abscessed. In addition, there were 3 cases of peri-urethral swelling without definite abscess formation, 1 paraphimosis, and 1 acute balanitis. The patients with posterior urethritis cleared just as readily as those with anterior urethritis. The complications epididymitis and prostatitis required a longer time before they became asymptomatic. Disappearance of the urethral discharge and symptoms took place in every one of the 947 cases by the fifteenth day after penicillin therapy; 916 had no discharge by the fifth day, and the majority of these were dry within 3 days.

The remaining cases were free of their gonorrhœa from 5 to 15 days, with the urine clearing about the same time as the urethral discharge disappeared. In every instance, smears and cultures taken the day following penicillin therapy were negative for gonorrhœa and remained negative in practically all throughout the period of hospitalization. Even though the smears were negative a watery discharge persisted for three days in the majority of cases and longer in many. Several patients with a continued urethritis disclosed a positive smear on one occasion, and this finding could not be confirmed by further study. This type of case would become cured without further treatment. The other type of persistent discharge which does not show any evidence of gonorrhœa can be treated by dilatation of the urethra, and is usually due to stricture in the anterior urethra. Only a few of these were found. Many of the cases of gonorrhœa had smears taken during and immediately after treatment, but the results were so variable that it was considered of no value over the regular smear examined 12 hours after treatment. Some of the cases had negative smears after as little as 40,000 units of penicillin, whereas many disclosed positive smears immediately after penicillin therapy.

In patients with prostatitis, whether acute, chronic, or abscessed, smears and cultures of the prostatic fluid were negative for gonorrhœa by the seventh day after penicillin therapy in all except 4; the latter were normal before the fifteenth day. Rectal examinations of the prostate were normal by the tenth day in all but 4 cases which persisted for a somewhat longer time.

In the patients with an acute epididymitis, the swelling entirely receded in 25 instances at the end of one week, and in 15 others by the end of the second week. The three instances of peri-urethral induration were all normal 5 days after treatment. The other complications did not interfere with successful therapy.

Briefly, 947 cases of gonorrhœa were free of active evidence of the disease one day following penicillin therapy, but the evidence of tissue destruction and elimination of cellular débris took about seven days or slightly longer to disappear.

The group of cases requiring more than 100,000 units of penicillin comprised 5·3 per cent of the total number and has been carefully studied in an effort to determine why the cases required additional penicillin for cure. All patients in this group, 53 in all, had negative smears and cultures for gonorrhœa after final treatment.

It was found that 30 of these cases revealed only an anterior urethritis, whereas 23 had a posterior urethritis in addition. In only 2 cases were complications noted: both had acute epididymitis, with one also having prostatitis. Two patients developed an acute epididymitis two days after the completion of their first 100,000 units of penicillin. Their complications subsided rapidly after their second course of penicillin. Following the first treatment with penicillin, the urethral discharge disappeared within 4 days and then recurred in 31 cases, but in 22 it persisted until completion of the second course. Smears of the urethral discharges were all negative the morning following the first penicillin treatment, but became positive for gonorrhœa again as follows: 4 on the second day, 12 on the third day, 6 on the fourth day, 6 on the fifth day, and the others varying up to as late as 21 days. In many of these latter cases it was not possible to check the time of recurrence accurately, as they had been treated previously in other hospitals and had been returned to duty. In connexion with the two patients' recurrences in the third week, there had been no evidence of gonorrhœa until follow-up examination disclosed that the culture obtained after prostatic massage was positive for

gonorrhœa. After first noting a positive recurrence, a second course was not administered until at least two repeated smears, or cultures, were found to be positive. As a result, further penicillin therapy was rarely given until seven days after the initial treatment.

Response to the second course of penicillin was satisfactory in all except 3 cases, which required a third course before becoming free of gonorrhœa. The urethral discharge had disappeared by the third day in 42 cases and by the seventh day in the remaining 8 cases, but 3 recurred again. Four cases of epididymitis, including the 2 which developed after the first course of penicillin, had completely subsided four days after the second course of penicillin.

Three cases which received a third course of penicillin had a recurrence of urethral discharge, with a positive smear, four days after their previous therapy, and when given 200,000 further units of penicillin, remained free from gonorrhœa.

Cultures of the urethral discharge were taken in 16 of the 53 cases which did not respond satisfactorily to initial penicillin therapy, and sensitivity tests were made. All of these 16 cases, including 2 receiving three courses of penicillin, had gonococci which were still sensitive to penicillin.

DISCUSSION

It is of interest to speculate why 5·3 per cent of this series required an additional amount of penicillin before satisfactory results were obtained. No definite cause could be discovered for the persistence of the gonorrhœa. The incidence of previous gonorrhœa or the quantity or type of prior treatment did not vary appreciably from the larger group, and the different lots of penicillin used were checked for potency, and were found to be of normal activity. There were no strains of gonococci in any of these cases which were resistant to penicillin. All were sensitive when tested in the laboratory. However, in some recent cases, which have had three courses of penicillin without success, it was thought that a resistant strain might be present. Until further study, this cannot be definitely reported. It was assumed, then, that the need for further penicillin therapy could probably be based on the varying degrees of sensitivity of some strains of the *Neisseria gonorrhœæ* to penicillin. As an adequate bacteriostatic level was obtained in those cases tested, it was assumed to be important to extend the duration of treatment when giving larger doses of penicillin the second or third time.

When the urethritis persisted more than five days without evidence of clearing, it was considered wise to investigate the urethra and prostate.

Toxicity.—No severe reactions were noted from the use of penicillin, though several patients ran a slight temperature which subsided after several hours.

Follow-up.—At the present time 15 per cent of the patients have to date returned for follow-up examination. In two instances previously described, the prostate still harboured the gonococcus. All the remaining cases disclosed negative cultures of the prostatic fluid four weeks following penicillin therapy. There has been no evidence of a recurrent urethral discharge, and urine analysis proved negative when examined at weekly intervals.

SUMMARY

1. 1000 cases of sulphonamide-resistant gonorrhœa were treated with penicillin, with satisfactory results.

2. 94·7 per cent were free of gonorrhœa after one course of treatment of 100,000 units of penicillin, given intramuscularly in 10,000-unit doses every hour or in 20,000-unit doses every three hours.

3. 5·3 per cent of this series required a second course of penicillin varying from 100,000 to 150,000 units. Three of these cases required a third course.

4. 7 per cent of the 1000 cases had developed complications other than posterior urethritis. Penicillin therapy hastened recovery in this group, in which only two patients received more than 100,000 units of penicillin.

5. There were no serious toxic reactions.

6. 15 per cent of patients were followed up for four weeks; 2 recurrences were noted. (These included cases receiving two courses.)

ACUTE GONORRHŒA, PREVIOUSLY UNTREATED

Selection of Cases.—The only patients with acute gonorrhœa considered for immediate penicillin therapy were those soldiers holding important positions, whose hospitalization would be detrimental to the best operation of their units. Included in this group were mostly air-crews.

Method and Dosage.—20,000 units of penicillin were given intramuscularly every two hours and also every three hours for 5 doses for a maximum of 100,000 units.

Duration of the Disease.—All these cases were seen shortly after development of a urethral discharge before any type of treatment had been initiated. The average time that they came to the hospital was about three days; individual variation from one to thirty-nine days.

Management of Cases.—Seventy-two patients were hospitalized averaging 5·9 hospital days, while 28 were treated on an out-patient status, spending eight hours at the clinic. Those remaining in the hospital were checked before leaving and those who received clinic therapy were followed by their own unit surgeon.

Laboratory.—The presence of gonorrhœa was confirmed by a Gram stain of the urethral discharge before treatment. After receiving penicillin, all hospitalized patients had to demonstrate

three negative smears and one negative culture at 24-hour intervals before returning to duty.

Results of Treatment.—One hundred cases of acute gonorrhœa received 100,000 units of penicillin with satisfactory results in all. However, there were 3 cases which required a second course of penicillin; 1 recurred while in hospital, the other 2 were discovered in routine follow-up examination 4 weeks after therapy. These 3 cases responded successfully to their additional treatment. Two complications, both epididymo-orchitis, resolved within 9 days after receiving penicillin. All smears were negative for gonorrhœa within 24 hours and the watery discharge disappeared within 48 hours in the majority of cases. Patients in this group in whom the urethritis persisted more than 48 hours, were found to have a soft anterior urethral stricture, which responded readily to dilatation.

DISCUSSION

In the treatment of these acute cases of gonorrhœa, the response to one course of 100,000 units was excellent, only 3 cases needing additional penicillin. The watery urethral discharge which persisted in many cases could usually be cleared up by adequate dilatation of the urethra when a stricture was present.

Just as satisfactory results were obtained in patients treated on an out-patient basis as in the hospital, if the former group were carefully checked by their own unit surgeons on return to duty.

One fact that has been noted in this group of cases is that the development of primary or secondary syphilis may be inhibited by the early use of penicillin, and that a diagnostic test for syphilis should be performed every month for at least five months. This observation is based on 5 patients who developed a positive Kahn reaction two months after penicillin therapy for gonorrhœa, and who had shown no primary or secondary lesions and in whom repeated Kahn tests had been negative up to that time.

Toxicity.—One patient developed a temperature of 101° after 60,000 units of penicillin had been given. It subsided in four hours.

Follow-up.—All cases were seen thirty days after treatment for prostatic smear and culture. All were negative for gonorrhœa with the exception of the 2 cases previously mentioned.

SUMMARY

1. 100 cases of acute gonorrhœa, previously untreated, received penicillin therapy with satisfactory results.

2. 97 per cent of these cases responded successfully to one course of 100,000 units of penicillin, and only 3 per cent required an additional 100,000 units.

3. 2 per cent of the cases had complications, epididymo-orchitis, in which recovery was shortened.

4. There were no serious toxic reactions.

5. 100 per cent of the cases returned for follow-up examination and 2 per cent were found to have active disease in the prostate still. (Those 2 cases were included with those receiving two courses of penicillin.)

CONCLUSIONS

It may be concluded that penicillin is the most effective agent we have for treating all types of gonorrhœa. If the supply were unlimited it would be the therapy of choice. It must be remembered that 100,000 units will not cure all cases, and that recurrences are possible. In cases not responding to two courses of penicillin, a careful study of the genito-urinary tract should be made. A high standard of cure should be maintained with a careful follow-up examination at least four weeks after penicillin treatment.

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PENICILLIN THERAPY FOR SYPHILIS*

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On the basis of the observation by Mahoney et al. (1943, a) that penicillin has marked spirochæticidal effects in both rabbit and human syphilis, 15 patients with early syphilis were recently treated with penicillin at a general hospital in the European Theatre of Operations. Penicillin therapy for syphilis is under study in several large syphilis clinics in the United States at the present time, but the results have not yet been published. Our study was undertaken to determine the practicability of this method of treatment in fixed and mobile medical units in a foreign theatre. This report will deal only with the immediate effects of treatment, and early follow-up serological studies, since insufficient time has elapsed to allow any prediction as to the eventual cure of the syphilitic infection in these patients.

Mahoney et al. treated 4 male patients, each of whom had a single penile chancre, by injections of 25,000 units of penicillin at intervals of four hours until a total of 1,200,000 units had been given. The number of injections was 48, and the

* A report of this study was presented before the Section of Medicine, Royal Society of Medicine, on March 28, 1944.

total period of treatment eight days. Spirochætes of syphilis were present in the lesions of all 4 patients before treatment, but were not demonstrable after sixteen hours of treatment. All Mahoney's patients had positive serologic tests for syphilis (S.T.S.) before treatment was begun. The time elapsing before the S.T.S. reverted to negative varied in each patient according to different antigens which were employed, but, using the Kahn standard test for comparison, the S.T.S. became negative in all four patients in 30, 36, 37, and 51 days, respectively. All four patients showed evidence of a Herxheimer reaction, consisting of pain or tenderness in the local lesion and the associated lymph-nodes, general malaise, mild headache, and temperature elevation not in excess of 2° F.

Prolonged therapy for syphilis by standard methods, employing alternate courses of an arsphenamine and a heavy metal, is productive of a reasonably satisfactory percentage of cures in patients whose treatment is completed according to schedule. However, such methods have many drawbacks which militate against their effectiveness, including minor and major reactions to treatment, the long period of time required, the necessity for skilled technique in the administration of injections, and, above all, the necessity for maintenance of regular continuity of treatment. In civilian clinics in the United States the percentage of patients who complete the outlined course of treatment for syphilis without significant lapse therefrom is stated to vary between 20 and 80 per cent, depending upon the effectiveness of follow-up methods in various clinics and the type of patient personnel (1942). Military personnel, while subject to rigid control, often cannot be treated for syphilis according to schedule under conditions of global warfare and rapid movement of troops. In combat, when the medical officer is hard-pressed by the treatment of urgent surgical casualties and disabling medical diseases, and the soldier engaged in a fight for life which prevents his reporting for frequent injections, the routine treatment of syphilis becomes impossible of accomplishment.

The development of a method of treatment which can be given within a short period of time is, therefore, a subject of pressing importance in military medicine. In April, 1943, intensive arsenotherapy for early syphilis was initiated in certain U.S. Army hospitals in the European Theatre of Operations. Over 2000 patients with early syphilis have been treated without mortality by this method, using a schedule in which a total of 20 mg. per kilo of body-weight of mapharsen and a total of 1·6 g. of bismuth subsalicylate are given in a period of 20 days. This method has the advantage of assuring completion of treatment in 95 per cent of patients on whom it is started, and apparently produces cure of the disease in between 85 per cent and 90 per cent. However, it must be given by medical officers with special training in syphilotherapy if excessive reactions to treatment are to be avoided, and an average stay of 25 days in hospital is necessary. Intensive arsenotherapy may be compressed into a period shorter than 20 days, but only at the risk of a mortality from treatment which, in our opinion, is excessive.

The patients selected for treatment with penicillin in this study were all from non-combatant units, in order that adequate serological and clinical follow-up could be assured. The types of early syphilis treated are outlined in the table.

Two schedules of treatment were employed. *Neither is presented as being optimum for all types of early syphilis*, and more recent information would indicate that larger amounts of penicillin will be required to obtain the maximal cure-rate possible with penicillin. Five patients received an injection of 20,000 units of penicillin intramuscularly every four hours, night and day, until a total of 1,000,000 Oxford units had been administered during a period of just over eight days. Ten patients were given an injection of 20,000 units of penicillin every four hours until a total of 500,000 units had been given in a period of four days.

The immediate effects of treatment may be summarized briefly :—

Herxheimer reaction: Two of the fifteen patients treated with penicillin had brisk Herxheimer reactions consisting of fever of 103° and 101°, respectively, between 8 and 12 hours after the initial injection of penicillin (*Fig.* 128). In

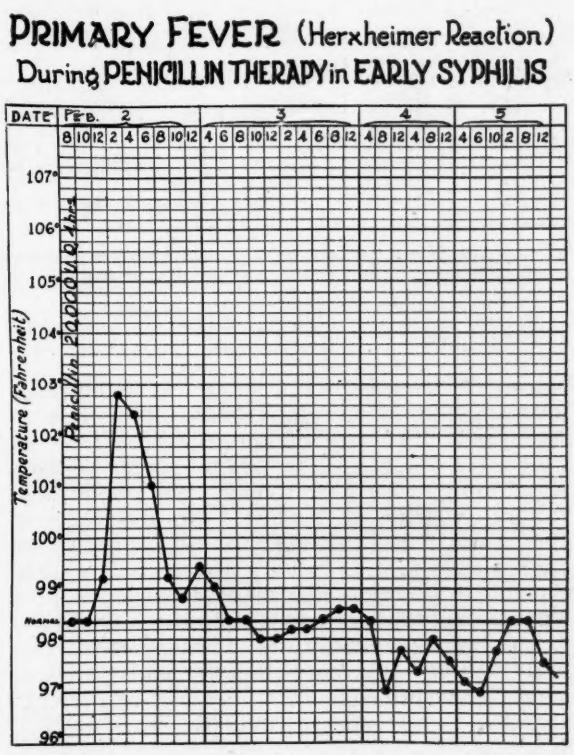

FIG. 128.—Febrile Herxheimer reaction following penicillin therapy in secondary syphilis (*Case* 1). This reaction did not interfere with continuance of treatment.

both of these patients, also, marked accentuation of the presenting lesions of syphilis became evident on the day following the initial treatment, one being a faint macular eruption which became prominent and 'measly' in appearance, and the other a chancre of the lip which increased considerably in size. Seven patients had oral temperatures of 100° F. within 12 hours after the initial injection of penicillin; 6 patients had no fever. None of these Herxheimer reactions interfered at all with continuance of treatment.

Disappearance of T. pallida: Thirteen of the fifteen patients had lesions from which *T. pallida* could be demonstrated, and the rate of disappearance of the organisms was determined by dark-field examinations done at intervals of two hours during the first day of treatment. In all but one patient spirochætes were not recoverable 14 hours after treatment was begun. In this patient the next examination was not done until 10 hours later, and spirochætes were not then demonstrable.

Healing of the lesions: The time required for healing of lesions of early syphilis is difficult to express on the basis of a single criterion for all cases. The induration of fleshy lesions may, for instance, require a comparatively long time to disappear. The rate of epithelization, i.e., the time after which a lesion was no longer 'open', was found to be a reasonably exact and satisfactory criterion of healing. On the basis of this, it was found that the time for healing varied from 3 days to 7 days, with a mean of 4·5 days. Satellite or generalized adenopathy subsided more slowly. All types of superficial lesions, including 'clean' and secondarily infected chancres, macular and papular secondary lesions, and peri-anal condylomata healed more rapidly than after arsenotherapy. This was particularly striking and impressive to any observer who had had considerable experience with conventional methods of treatment.

Blood serological tests: Quantitative Kahn tests were performed daily or every other day during the period of observation of the patients in hospital. There were no changes during this time that could be regarded with certainty as outside the limits of error of the method, but it is believed that study of a larger series of patients in this regard would probably demonstrate a tendency for the reagin titre to increase during the period of treatment. The serological tests for varying periods after completion of treatment are given in the table.

The period of observation following treatment does not exceed 12 weeks in any patient. The serological trend has been satisfactory in all cases with the possible exception of *Case* 15, in which a quantitative test was not done at the last follow-up examination. On further observation, should a confirmed significant increase in the Kahn titre be observed at any time, or clinical relapse develop, or the Kahn remain persistently positive six months after completion of treatment, it is planned to give further penicillin therapy, using a total dosage of over 2,000,000 units for the second course. Spinal fluid examinations will be done in all patients six months after completion of the initial course.

Patient	Type Syphilis	Total Amount of Penicillin	Kahn during Treatment	Kahn Weeks after Treatment
1	Secondary	1,000,000	Pos., 160 units*	7 wk. Neg.
2	Primary	500,000	Pos., 4 units	7 wk. Neg.
3	Primary	500,000	Pos., 4 units	6 wk. Neg.
4	Primary	500,000	Pos., 40 units	3 wk. Neg.
5	Primary	1,000,000	Neg.	10 wk. Neg.
6	Primary	500,000	Pos., 4 units	7 wk. Neg.
7	Secondary	1,000,000	Pos., 40 units	7 wk. Pos., 20 units
8	Secondary	500,000	Pos., 80 units	3 wk. Neg.
9	Primary	1,000,000	Pos., 20 units	10 wk. Neg.
10	Primary	500,000	Pos., 20 units	4 wk. Neg.
11	Primary	500,000	Neg.	2 wk. Neg.
12	Primary	1,000,000	Neg.	3 wk. Neg.
13	Primary	500,000	Pos., 40 units	3 wk. Pos., 20 units
14	Primary	500,000	Neg.	2 wk. Neg.
15	Primary	500,000	Pos., 20 units	6 wk. Pos.

* The quantitative units are expressed according to the method outlined in Technical Manual, 8–227, Methods for Laboratory Technicians, War Department, Washington, 1941, Oct. 17. The number of units is obtained by multiplying the dilution of serum in the tube by 4, i.e., a tube showing flocculation with a serum dilution of 1 : 20 would be recorded as indicating a reagin level of 80 units.

DISCUSSION

Several advantages of penicillin therapy for early syphilis are evident on the basis of this small series of patients: (1) The involution of all types of lesions of early syphilis is astonishingly prompt. (2) Penicillin causes a prompt and rapid disappearance of spirochætes from infectious cutaneous lesions of early syphilis. Sterilization of these lesions is as least as rapid as that observed during mapharsen therapy. (3) Treatment was given to these patients without any reactions of a severity sufficient to interfere with completion of treatment. In this respect penicillin therapy has a marked advantage over intensive arsenotherapy. (4) The technique of administration is simple, and may be carried out by any reasonably trained technician.

Certain considerations of importance in this method of treatment are apparent, and there are many points on which further information is needed. Obviously the first and most important is the evaluation of the final effectiveness of penicillin alone in preventing relapse and progression of the syphilitic infection. No information on this point is available from this series of cases, but a reasonable evaluation may be expected from more extensive studies elsewhere in the near future. There seems no question that penicillin will occupy an important, if not absolutely pre-eminent, position in the therapy of syphilis in the future.

One disadvantage of Mahoney's schedule of treatment is the necessity of administering the drug at frequent intervals on a round-the-clock basis. If the preferable technique of penicillin therapy in bacteræmias offers any corollary, it would indeed be preferable to administer penicillin for syphilis at intervals of two hours, in order that a more even blood-level might be maintained. Evaluation of the necessity for frequent administration of penicillin for syphilis is of great practical importance in military hospitals, since the necessity of treating a large number of patients at night may lead to very considerable dislocation of the duty schedules of personnel. The theoretical advantage of a vehicle which would allow slow steady release of penicillin from the site of the injection is apparent.

A further consideration of importance in regard to penicillin is the fact that it is the only drug which is highly effective against both syphilis and gonorrhœa. One of us (D. M. P.) has observed two patients in whom the treatment of gonorrhœa with a total of 100,000 units of penicillin apparently suppressed a coincident syphilitic infection, with delay in the appearance of secondary lesions. Examination of a patient with gonorrhœa should include a careful search for lesions of early syphilis. A far too frequently encountered tragedy of syphilotherapy in the past has been the administration of an arsenophenamine before the diagnosis of syphilis had been definitely confirmed, with consequent often irrevocable clouding of the diagnostic picture thereafter. Care should be exercised to avoid the unwitting production of a similar state of uncertainty by the administration of penicillin for gonorrhœa in the presence of very early lesions of syphilis. A serological follow-up examination should be done after penicillin treatment of gonorrhœa after a longer interval than the two months previously considered adequate.

If, as seems entirely possible, penicillin alone will produce a biological cure of the syphilitic infection in a considerable proportion of patients treated, the vulnerability of the patient to reinfection will be proportionately increased. This has been a matter of practical importance in connexion with intensive arsenotherapy, in which biological cure of syphilis is frequently obtained. Reports have been received of at least six patients who have undergone intensive arsenotherapy and who have later developed penile lesions under findings and circumstances fulfilling reasonable criteria for reinfection.

SUMMARY

Experience with penicillin therapy in early syphilis in 15 patients has confirmed the report of Mahoney et al. (1943, a) on the rapid spirochæticidal effect of penicillin in man, the prompt regression of early lesions of syphilis, and the absence of significant reactions to treatment. No conclusions as to the optimum dose of penicillin, the most effective time-dose relationship, or the final curative effect of treatment can be drawn from this study. The method of treatment offers possibilities of great importance in the management of syphilis occurring in military personnel, since prolonged treatment with arsenic and bismuth is impossible to carry out continuously under many conditions in a Theatre of Operations, and since the immediate effects of penicillin therapy are superior to those observed after intensive arsenotherapy.

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